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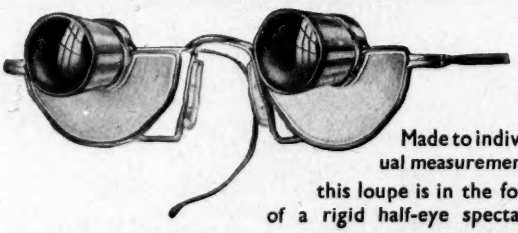

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Brit. J. Ophthal. (1957) **41**, 193.

COMMUNICATIONS

THE FELLOW EYE IN ACUTE CLOSED-ANGLE GLAUCOMA*

BY

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THIS PAPER deals with a series of 200 cases of acute unilateral closed-angle glaucoma, which were examined with a view to establishing a basis for assessing the treatment of the fellow eye.

The investigation of a series of over 3,000 cases of glaucoma of all types at the Glaucoma Clinic of the Institute of Ophthalmology has shown that miotic treatment is no sure guard against the occurrence of an acute attack in the second eye. A patient on miotic therapy may be relieved of his symptoms, for example, by pilocarpine 1 per cent. thrice daily, and yet may have a pathological rise of tension under provocative tests. Consequently such a person is in an unsafe situation; he may get an acute attack in this eye in a moment of vasomotor instability, or he may develop chronic closed-angle glaucoma with eventual peripheral anterior synechiae and cupping of the optic disc.

Of recent years, a plea for peripheral iridectomy as a treatment for very early closed-angle glaucoma and as a prophylactic measure has been ably put by Chandler (1952), Chandler and Trotter (1955), and by Barkan (1937, 1938, 1939, 1954). These authors have clearly defined the indications and contra-indications for this relatively simple procedure.

For the purposes of this investigation, acute closed-angle glaucoma has been defined as an attack of tension in this type of the disease sufficiently severe to warrant an intensive course of treatment with eserine on arrival at the hospital. Similarly, the term "bilateral onset", which appears in some of the Tables, refers to those cases which arrived at hospital with both eyes affected.

Of these 200 cases, 110 come from the files of the Institute of Ophthalmology, and ninety from those of the Westminster Branch of Moorfields.

Material

The average age of all the patients in the series was 59 years (range 87–27). 45 (29 per cent.) were men and 155 (71 per cent.) were women, a sex distribution which agrees with that in other published series.

Of the cases not subjected to operation, 122 were followed-up for 5 years or less, 37 for 5 to 10 years, and only seventeen for more than 10 years. Three of the

* Received for publication December 18, 1956.

Institute patients are known to have died; those from the hospital files were all alive at the end of 1955.

With an average age of 58·4, it seems likely that some patients do not live long enough for the second eye to become affected, and the question arises whether glaucomatous subjects have a higher mortality than the rest of the population. Bennett (1955) published an interesting survey which sheds some light on this matter. He compared the mortality for all cases of glaucoma with that for the rest of the local population and found no significant difference between them.

The second eye may undergo an obvious acute attack or prodromal signs and symptoms may occur. For the purposes of this paper these signs have been defined as:

(*i*) a clear history of rainbows round lights, blurring of the vision, and pain in or around the eye,
(*ii*) a raised ocular tension found on routine tonometry,
(*iii*) positive provocative tests, with or without symptoms.

The cases derived from the Institute have had provocative tests, but those from the hospital have not.

Ten of the Institute cases out of sixty in which the second eye was symptom-free have shown positive provocative tests but have not complained in any way of their apparently normal eye. The dark-room test was the usual provocative test employed; it is generally thought to be positive in 60 per cent. of cases of closed-angle glaucoma, but recent work shows that this is probably too high an estimate.

This lack of reliablility of the dark-room test suggests that the proportion of ten out of sixty cases is too low; moreover, no provocative tests were applied to the hospital series, and it seems at least probable that they would also show a proportion of positive results in apparently normal eyes. It seems therefore that the figures for prodromal symptoms submitted below may be too low, and that a markedly higher number of patients would have been placed in this category if they had been submitted to a provocative test of 100 per cent. reliability.

Table I shows that, of these 200 cases, only seven had a prophylactic operation on the second eye, while seventeen patients had both eyes affected simultaneously. In none of the eyes subjected to surgery did a straightforward primary angle-closure glaucoma occur. This leaves 193 cases, and in these the second eye has been involved in 102 (53 per cent.).

TABLE I
ANALYSIS OF CASES

Treatment	No. of Cases	Second Eye Involved	
Prophylactic Operation ...	7		
Bilateral Onset	17		
Miotic Therapy	137	85 *ex* 176 = 48 per cent.	102 *ex* 193 = 53 per cent.
Untreated	39		
Total	200*		

* Average age 58·4 yrs.

Excluding those patients who suffered a simultaneous onset in both eyes, the second eye was involved in 85 out of 176 (48 per cent.).

TABLE II
FATE OF FELLOW EYE

Cases	No.	Percent.
Acute Attacks	50	28 (35)
Prodromal Symptoms ...	35	20 (18)
No Symptoms yet ...	91	52 (47)
Total	176	100 (100)

Table II shows the number and percentage of those who had acute attacks or prodromal symptoms in the second eye, and those who did not.

The total of those who had neither a bilateral onset nor a prophylactic operation is 176. The percentages in brackets include the bilateral cases, and are put in to complete the picture of the non-operated cases in the series.

It may be repeated here that the patients who had a prophylactic operation were excluded because none had an acute attack or "prodromal symptoms" of the precise kind defined above.

On the other hand, fifty of the remainder, including both treated and untreated cases, had an acute attack in the second eye. Even more striking is the fact that of the 137 patients treated with miotics, 29 (21 per cent.) had a second acute attack, and 25 (18 per cent.), developed "prodromal symptoms" (Table III).

TABLE III
RESULTS OF TREATMENT

Treatment	2nd Acute Attack	Symptoms	No Symptoms	Total
Nil	21	10	8	39
Pilocarpine	18 } 29	18 } 25	67 } 83	103 } 137
Eserine	11 }	7 }	16 }	34 }
Total	50	35	91	176

The results of treatment are shown in Table IV (overleaf) under three headings. The miotic-treated groups have not been further subdivided according to the strength of miotic, first, because patients tend to be given weaker miotics the longer they survive without symptoms, and secondly, because if a patient has the anatomical and vasomotor pecularities which predispose him to another acute attack, a routine miotic two or three times a day will often not prevent it occurring. There are patients in this series who have had an acute attack despite the use of 1 per cent. eserine.

Table IV shows that, of 39 untreated cases, 31 (78 per cent.) had an acute attack (21) or prodromal symptoms (10) in the second eye. In another series of nineteen untreated cases described by Winter (1955), seventeen (89 per cent.) developed symptoms.

The apparent difference in the incidence of prodromal symptoms in patients treated with pilocarpine and with eserine is not statistically significant, being due to the difference in size between the two series.

TABLE IV
PERCENTAGE RESULTS

Treatment	No. of Cases	2nd Eye Involved	
		No.	Per cent.
Nil	39	31	78 {54 Acute Attacks; 24 Symptoms}
Pilocarpine	103	36	34 {17 Acute Attacks; 17 Symptoms}
Eserine	34	18	53 {32 Acute Attacks; 21 Symptoms}
Total	176	85	48

Pilocarpine *v.* Eserine $\chi^2 = 3{\cdot}46$; $0{\cdot}5 > p > 0{\cdot}1$
Miotics *v.* No treatment $\chi^2 = 19{\cdot}5$; $p > 0{\cdot}001$
} for one degree of freedom

On the other hand, the difference between treated and untreated patients who developed symptoms is highly significant.

Hence, although miotics will not prevent the onset of acute or subacute symptoms in the second eye, they may in some cases convert a potential acute attack into a chronic closed-angle glaucoma.

The 85 patients who had another acute attack or "prodromal symptoms" were examined to see if there was any difference in the time of onset of symptoms as between treated and untreated cases (Table V).

TABLE V
RESULTS, BY LENGTH OF FOLLOW-UP

Length of Follow-up (yrs)	Symptoms		No Symptoms	
	No Miotic	Miotic	No Miotic	Miotic
Up to 5 ...	20	47	2	53
6–10 ...	7	6	4	20
11–15 ...	1		2	5
16–20 ...	2	1		4
20+ ...	1			1
Total ...	31	54	8	83

Table VI (opposite) sets out the same information in slightly different fashion. The percentage of patients developing symptoms diminishes as time goes on, which seems to suggest that the longer a patient survives without trouble in the second eye the less likely it is to develop.

On the other hand, one patient in this series had an acute attack in the second eye 32 years after that in the first. She had had no treatment and had not appeared for follow-up during this period. The average period which elapsed before

TABLE VI

Length of History (yrs)	Symptoms	No Symptoms	Percentage with Symptoms
Up to 5	67	55	55
6–10	13	24	38
10+	5	12	29

symptoms developed in the second eye in untreated patients was 5·7 years; in those treated with eserine it was 3·5 years, and in those on pilocarpine it was 3·7 years. There is no statistically significant difference between these groups, since there were only 39 untreated cases four of which took more than 15 years to develop symptoms, while the treated cases number 137.

The average period which elapsed before symptoms developed, taking treated and untreated cases together, was 4·25 years.

Table VII shows in some detail the seven cases which had a prophylactic operation in the second eye. They form a small series but their record is good.

The first five patients (one peripheral iridectomy and four trephines) have open angles with normal tension and normal optic discs. They have remained symptom-free up to now, and there seems no reason for supposing that they will not remain so.

The last two patients (both trephines) are just beginning to develop trouble after 12 and 24 years respectively.

TABLE VII
PROPHYLACTIC OPERATIONS TO THE SECOND EYE

Prophylactic Operations	Numb	Duration of Trouble-Free Period (yrs)
Peripheral Iridectomy	1	3
Trephines	4	6, 6, 10, and 11
	1	12→peripheral anterior synechiae T+
	1	24→cupping of disc

The patient with the 12-year history has an angle that is almost totally closed by peripheral anterior synechiae. As he has been symptom-free for so long it is almost certain that most of these date from his operation. There was probably delay in the re-formation of the anterior chamber, which is unavoidable in a proportion of cases undergoing a filtering operation. It is suggested that he is suffering from one of the defects of a trephine. His tension began to rise, and he has now had a further filtering operation.

The patient with the 24-year history still has an open angle, but is just beginning to develop cupping of the disc. It seems reasonable to suggest that this patient is beginning to develop simple glaucoma.

Discussion

The prognosis for the second eye may be summarized as follows:

(1) The fellow eye may not be glaucomatous, and in a few cases may never become so, but only constant surveillance will tell us this. If in any given case the eye is not going to become glaucomatous the instillation of miotics is a waste of time, although it would be a bold man who would assert this in the individual case.

(2) The eye may become glaucomatous at a later date, as did the majority in this series. Miotics are not a sure guard against this development, and in 29 cases did not even prevent a second acute attack. In 25 other cases symptoms of chronic angle-closure have set in in spite of miotics; many of these cases are apparently controlled on stronger doses of miotics, but how long they will remain so only time will tell. It seems likely that these patients if they live long enough, will either develop cupping of the disc through impaired filtration, or suffer the crisis of an acute or subacute attack.

(3) The eye may already have incipient glaucoma as shown by symptoms of pain, blurred vision, and haloes, or by positive provocative tests. Many patients with positive provocative tests have noticed no symptoms and are fortunate in having had their trouble diagnosed in this way. More cases would almost certainly be found to have glaucoma were a test of 100 per cent. reliability available to us.

(4) The eye may be undergoing an acute or subacute attack when the patient is first seen.

There seems, then, to be a good case for applying provocative tests to the second eye even when it is apparently normal clinically. The tests also help in assessing whether a manifest chronic closed-angle glaucoma may be partially controlled by a miotic at any given time.

There seems to be a better case for undertaking a peripheral iridectomy at any rate in younger patients, and in those whose occupation takes them away from surveillance for long periods. This operation is subject to fewer complications than any other glaucoma procedure. Properly done it should check the progress of peripheral iris bombé, peripheral anterior synechiae, and trabecular blockage, which lead eventually to cupping of the disc, and may at any time be interrupted by an acute attack.

Summary

(1) 200 patients who had suffered an attack of acute closed-angle glaucoma have been examined to discover the fate of the fellow eye.

(2) Excluding seven cases who had undergone a prophylactic operation, 53 per cent. developed symptoms in the other eye. In 35 per cent. the "symptoms" comprised another acute attack.

(3) There was no significant difference in the time taken to develop trouble in the second eye between patients treated with miotics and those who had no treatment.

(4) The second eye became involved after an average interval of 4·25 years regardless of treatment.

(5) The use of provocative tests for closed-angle glaucoma in symptom-free patients is re-emphasized.

(6) It is suggested that peripheral iridectomy is a safer guard against trouble than miotic therapy.

I acknowledge with pleasure Sir Stewart Duke-Elder's advice and criticism in the preparation of this paper.

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Brit. J. Ophthal. (1957) **41**, 200.

OBSERVATIONS ON THE DARKROOM TEST AND ITS MECHANISM*

BY

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Director of Research: Sir Stewart Duke-Elder

THE RISE in ocular tension after a period in the dark first noted by Grönholm (1910) was later developed as a provocative test by many different workers (Seidel, 1920; Serr, 1928; Sallmann, 1930; Ohm, 1936; Ross, 1953; Higgitt, 1954).

Conflicting opinions on the value of the darkroom test have been expressed, Higgitt finding that 78 per cent. of his cases of "congestive glaucoma" gave a positive rise in ocular tension with the test, while Leydhecker (*see* Duke-Elder, 1955) found that only 11 per cent. of his suspected congestive cases with narrow anterior chamber angles did so. Leydhecker wondered what should constitute a positive test, feeling that the rise of 9 mm. Hg suggested by Higgitt was probably somewhat low, and noting that no statistical analysis of the change in ocular tension to be found in normal eyes with the test had yet been published.

While some of the negative results with this test which have been reported in the past have undoubtedly been due to its use in cases of chronic simple glaucoma, there is no doubt that, even in cases of known closed-angle glaucoma, negative results with the darkroom test are not uncommon.

The present study of the darkroom test was originally undertaken so that the results might be compared statistically with those of the darkroom outflow test, details of which have already been published (Foulds, 1956). Several points of interest which might help to explain the mechanism of angle closure have however emerged, and these are presented here.

Material

The results reported are all of tests performed at the Institute of Ophthalmology as part of the routine work of the Glaucoma Clinic, the method used being similar to that described by Higgitt (1954). The eyes of the patient to be tested were anaesthetized by a drop of 1 per cent. amethocaine hydrochloride in each, and a measurement of the ocular tension was made with a standard Schiötz X-tonometer. The patient was then placed in the darkroom for one hour and at the end of this period a further measurement of the ocular tension was made with the same instrument as before. Both the initial and final measurements were made under normal room lighting.

* Received for publication December 3, 1956.

The analysis is based on the results of the test on a series of 57 normal cases and on 108 cases of clinically diagnosed closed-angle glaucoma. Before being assigned to the control series, the normal cases were all extensively studied; the case history was taken, the peripheral and central visual fields were recorded, and gonioscopy, tonometry, and an outflow test were performed on each. Only persons with no sign or symptom suggestive of glaucoma and only those without narrow anterior chamber angles were included in this group. In the closed-angle glaucoma series, all cases had some recognizable clinical stigma of the disease and all had narrow anterior chamber angles. From each group only one eye chosen at random from each patient tested was included in the series to be analysed, so that the similarity of fellow eyes might not minimize the variance of the series.

In order that the two series of cases should be comparable except with regard to the presence or absence of closed-angle glaucoma, it was necessary to ensure that the age and sex distribution within and between the two series should be similar. The proportion of males to females and the mean age of each group were calculated for the two series of cases, and no significant differences were found between the two series in these respects (Tables I and II).

TABLE I

COMPARISON OF SEX DISTRIBUTION IN 57 NORMAL CASES AND 108 CASES OF CLOSED-ANGLE GLAUCOMA

Series	Male		Female	
	No.	Per cent	No.	Per cent.
Control	32	56	25	44
Test	55	51	53	49

$\chi^2 = 0{\cdot}406$; $n=1$; $P=>0{\cdot}50$.

TABLE II

COMPARISON OF AGE DISTRIBUTION IN 57 NORMAL CASES AND 108 CASES WITH CLOSED-ANGLE GLAUCOMA

Series	Mean Age (yrs)		Comparison of Mean Ages of Males and Females	Total Mean Age (yrs)	Comparison of Total Mean Age in Control and Test Series
	Male	Female			
Control ...	55·7 (±13·0)	57·8 (±10·2)	$t=1{\cdot}11$ $n=55$ $P=>0{\cdot}10$	56·8 (±11·8)	$t=0{\cdot}433$ $n=163$ $P=>0{\cdot}10$
Test ...	57·4 (±10·4)	57·8 (±11·8)	$t=0{\cdot}18$ $n=106$ $P=>0{\cdot}10$	57·7 (±11·0)	

Table I shows the sex distribution of the two series; on analysis by a χ^2 test, there is no significant difference between the control and test series in regard to sex composition ($\chi^2=0{\cdot}406$; $n=1$; $P=>0{\cdot}50$). Table II shows the age distribution; the two series are comparable in this respect also. In the control series the mean age of the males (55·7 yrs

±13·0) does not differ significantly from that of the females (57·8 yrs ±10·2) ($t=1·11$; $n=55$; $P=>0·10$). In the test series the mean age of the males (57·4 yrs ±10·4) is not significantly different from that of the females (57·8 yrs ±11·8) ($t=0·18$; $n=106$; $P=>0·10$). In addition the mean age of all cases in the control series (56·8 yrs ±11·8) is not significantly different from that in the test series (57·6 yrs ±11.0) ($t=0·433$; $n=163$; $P=>0·10$).

Results of Investigation

The effect of darkness on the ocular tension of normal eyes was first studied, as it has been stated that there is a tendency for the test to produce a small rise in tension in such eyes (Duke-Elder, 1940; Higgitt, 1954).

In the present series a rise in ocular tension of 7 mm. Hg (Schiötz) was found in some normal eyes. The mean rise was small (+0·97 mm. Hg ±2·54) but statistically significant, as can be seen by comparing this value with the expected value of zero by Student's "*t*" test.† This small mean rise reflects the fact that 36 per cent. of the normal eyes tested showed a rise in ocular tension with the test, while only 9 per cent. showed a fall.

In the known closed-angle series, a well-marked rise in ocular tension occurred with the test (mean +11·12 mm. Hg ±12·08). A "*t*" test shows that this mean rise differs significantly from that in the normal series.‡

From the behaviour of the normal eyes it is possible to determine what rise in ocular tension should be regarded as a positive test. A rise of more than three times the standard deviation of the mean rise in the normal series could reasonably be regarded as a positive result, for such a rise could occur by chance less than once in a hundred cases. Three times this standard deviation (2·54) gives a rise of 7.62 mm. Hg above the mean rise found in the normal series (+0·97 mm. Hg), making a positive result a rise in ocular tension of at least +8·6 mm. Hg. If 95 per cent. confidence limits are applied to the mean rise in the normal series with the test, it is found that a positive result could lie between +7·8 and +9·4 mm. Hg.

This is in close agreement with the rise of +9 mm. Hg proposed by Higgitt as the measure of a positive result, although it would seem that the actual figure might in fact be a little lower than this author thought.

Value of the Darkroom Test

Of the 108 eyes with known closed-angle glaucoma, only 56 (51·9 per cent.) showed a rise of more than 8 mm. Hg, and of these seventeen had initial tensions already above "normal" limits (*i.e.* greater than 31 mm. Hg).

In order to determine whether there was a clear demarcation between the results in the control and glaucomatous series, the results in each series were classified according to the change in tension produced by the test (from −7 mm. Hg to +60 mm. Hg in 3-mm. steps); the number of results in each group was expressed as a percentage of the total number of tests in each

† ($t=2·89$; $n=56$; $P=<0·01$)
‡ ($t=6·26$; $n=163$; $P=<0·001$)

series. These results are represented graphically in Fig. 1, which shows that the two series overlap considerably, so that in many cases the test does not clearly separate the normal from the abnormal.

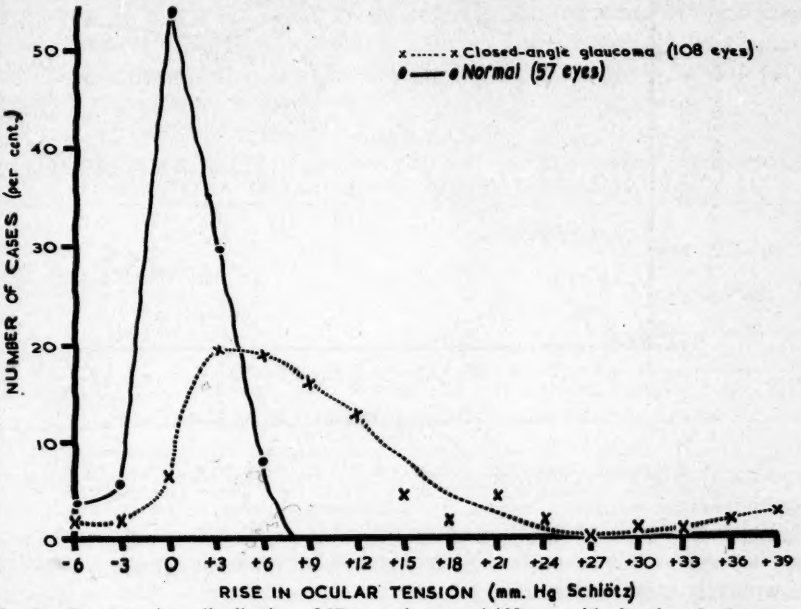
x ..... x Closed-angle glaucoma (108 eyes)
o —— o Normal (57 eyes)
NUMBER OF CASES (per cent.)
50
40
30
20
10
0
-6 -3 0 +3 +6 +9 +12 +15 +18 +21 +24 +27 +30 +33 +36 +39
RISE IN OCULAR TENSION (mm. Hg Schiötz)

FIG. 1.—Graph to show distribution of 57 normal eyes and 108 eyes with closed-angle glaucoma in relation to the change in ocular tension produced by the darkroom test. There is considerable overlap between the normal and glaucomatous results.

To establish whether the rise in ocular tension with the darkroom test in cases of closed-angle glaucoma was influenced at all by the ocular tension at the start of the test, the cases of closed-angle glaucoma were divided into groups according to the initial tension, and the mean final tension was determined for each group. When the mean final tension in these cases was plotted against the initial tension, it was found that for initial tensions of up to 25 mm. Hg and over 30 mm. Hg the test appeared to produce a mean increase in ocular tension of the order of 10 mm. Hg (Fig. 2, overleaf). The mean rise in tension in the group with an initial tension of 26 to 28 mm. Hg, however, was seen to be unexpectedly large (+26·1 mm. Hg). This suggested that positive results might be more frequently found in eyes with an initial tension in the region of 28 mm. Hg than in those with initial tensions above or below this level. To determine whether this was so, the proportion of positive results with the darkroom test occurring in groups of cases starting at different initial tensions was calculated for the cases of closed-angle glaucoma, and it was found that this proportion rose from approximately 45 per cent. of cases with an initial tension below 22 mm. Hg to 71 per cent. of those with

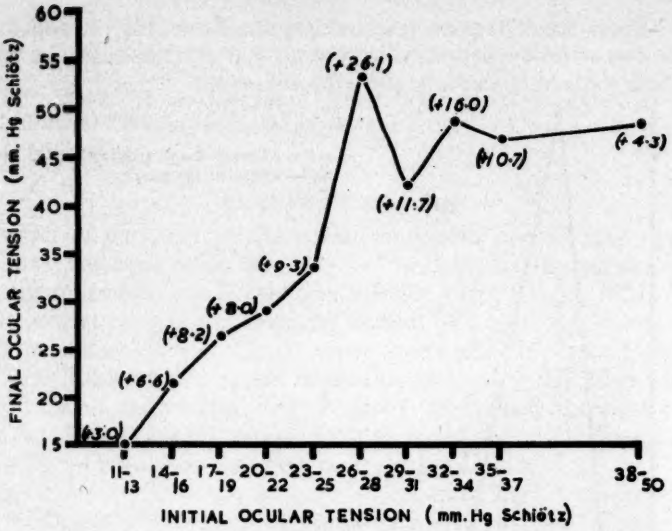

FIG. 2.—Graph to show relationship between initial and final ocular tensions of 108 eyes with closed-angle glaucoma submitted to the darkroom test. The rise in tension from an initial level of 26–28 mm. Hg is greater than that from any other initial ocular tension.

The figures in brackets represent mean changes in ocular tension.

an initial tension of from 26–28 mm. Hg, but fell again in cases with an initial tension that was higher still (Fig. 3).

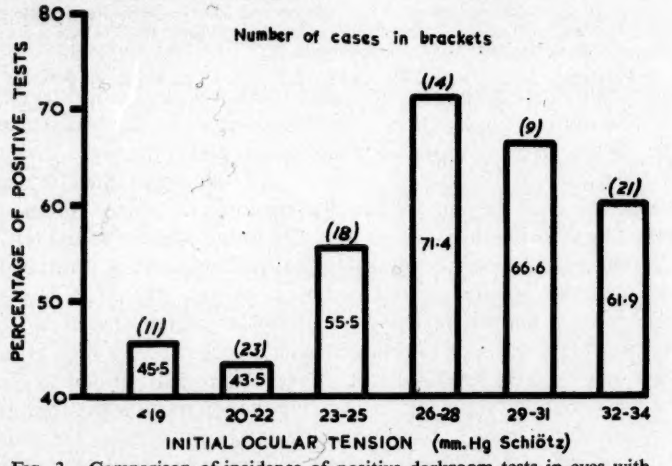

FIG. 3.—Comparison of incidence of positive darkroom tests in eyes with closed-angle glaucoma at different initial tension levels. The greatest number of positive tests occurs in the group with an initial ocular tension of 26–28 mm. Hg.

To establish whether these differences were real, the number of eyes showing

a rise of more than 8 mm. Hg from an initial tension of less than 25 mm. Hg was compared by a χ^2 test with the number showing a similar rise from an initial tension of 26–30 mm. Hg (Table III, below); 23 out of 32 tests on eyes with an initial tension of 26–30 mm. Hg showed a rise of more than 8 mm. Hg (71·9 per cent.) compared with seventeen out of 41 tests where the initial tension was below 25 mm. Hg (41·5 per cent.). The difference between these groups is significant.*

TABLE III

COMPARISON OF RESULTS OF DARKROOM TEST ON EYES WITH CLOSED-ANGLE GLAUCOMA AND DIFFERING INITIAL TENSION LEVELS

Initial Tension (mm. Hg)	Result of Darkroom Test		
	Positive		Negative
	No.	Per cent.	
Less than 25 (41 eyes)	17	41·5	24
26–30 (32 eyes)	23	71·9	9

$\chi^2=5{\cdot}54$; $n=1$; $P=<0{\cdot}02$.

It has already been noted that the mean rise in tension with the darkroom test in eyes with closed-angle glaucoma was greater where the initial tension was in the region of 28 mm. Hg (+26·1 mm. Hg) than from any other initial tension, where the rise was nowhere greater than +16 mm. Hg (Fig. 1). To determine whether this large mean rise in tension in the first group was significantly different from that occurring in the other groups, the mean rise in all cases with initial tensions of from 26–30 mm. Hg (+23·7 mm. Hg ±29·8) was compared with the mean rise from all other initial tensions together (+8·6 mm. Hg ±8·18). A "t" test shows that the former mean rise in tension differs significantly from the latter.† As this might merely mirror the fact that the group of eyes with low initial tensions had a smaller proportion of positive results than the other, the effect of the initial tension level on the magnitude of the rise produced by the test was calculated for the cases of closed-angle glaucoma which gave a positive result. Of 54 eyes showing a rise in tension of more than 8 mm. Hg ten had an initial tension of from 26–28 mm. Hg, while 44 had an initial tension either above or below this. The mean rise in tension for the former group was 34·8 mm. Hg (±15·8) compared with +14·8 mm. Hg (±8·9) for the latter. The difference between these mean rises in tension is significant.‡ It would appear, therefore, that, not only is the result of the darkroom test more likely to be positive where the initial tension in the tested eye is in the region of 28 mm. Hg, but also that the actual rise in tension to be expected is greater at this initial tension than at any other.

* ($\chi^2=5{\cdot}54$; $n=1$; $P=<0{\cdot}02$).
† ($t=4{\cdot}14$; $n=106$; $P=<0{\cdot}001$).
‡ ($t=5{\cdot}4$; $n=52$; $P=<0{\cdot}001$).

Discussion

In this investigation it was found that only about one half of all the cases of closed-angle glaucoma submitted to the darkroom test showed a rise in ocular tension of more than 8 mm. Hg.

The likelihood of an eye with closed-angle glaucoma giving a positive result with the darkroom test appeared to be related to the initial tension in that eye, and was greatest where the initial tension was in the region of 28 mm. Hg. In addition, the magnitude of the rise in tension produced by the test was also greatest at this initial ocular tension.

As has been pointed out by Barkan (1936), the angle of the anterior chamber is narrower above than below. More recently, evidence has been produced to support the view that, in cases of closed-angle glaucoma between hypertensive attacks, part of the angle of the anterior chamber is closed by irido-corneal contact, at first in the upper narrow part of the angle and later if at all in the lower, wider sector (Phillips, 1956). From the results of the darkroom test, it seems likely that an eye with a resting tension of between 26 and 30 mm. Hg has already much of the filtration angle blocked either functionally or organically, and that the darkroom test in such an eye will rapidly close most of the remaining open sector to give a large rise in ocular tension. Where the angle is not so obstructed before the test, much of the time in the dark may be taken up by the gradual closure of the filtration angle from above downwards, and only if this causes the closure of a sufficient area of the filtration angle within the time allowed for the test will the tension rise appreciably. It is noteworthy that a few cases in which the result of the darkroom test was negative after one hour gave a significant rise in ocular tension after 2 hours in the dark. In addition, outflow measurements in cases of closed-angle glaucoma tend to be low where the ocular tension is above 25 mm. Hg, supporting the view that a certain amount of angle obstruction exists although the tension may still be within the accepted limits of normality. The great difficulty in differentiating an obstructed angle from a narrow but still functioning one, and the fact that light, by constricting the pupil, tends to re-open the filtration angle, limits the value of gonioscopy in the study of these cases; nevertheless, direct examination by this method supports the view that a positive result with the darkroom test is accompanied by complete or almost complete closure of the angle of the anterior chamber (Ross, 1953; Higgitt, 1954).

An eye with closed-angle glaucoma which shows a tension of over 25 mm. Hg may be regarded as being in an unstable state and liable to develop an acute rise in tension. If this is so, it follows that an eye under treatment with miotics for closed-angle glaucoma which frequently has a tension in the upper reaches of normality may in fact be developing organic occlusion of the angle and would be better treated surgically.

From what has been said, it would appear that in the early case of closed-angle glaucoma, the result of the darkroom test is more likely to be negative

than positive, and that, though a positive result is of course of great value in such a case, a negative result does not in any way rule out the existence of the disease.

The fact that definite though small rises in ocular tension occur in some normal eyes is of great interest. In the control cases described above angle closure is most unlikely to have occurred with the test, as none of the control eyes had a narrow angle; nor did gonioscopy show angle closure in those normal eyes examined after the test. It has been shown in addition (Foulds, 1956) that there is no significant alteration in the facility of aqueous outflow in normal eyes during the darkroom test. It would appear therefore that this rise in tension in the normal eye is due to some change either in the rate of aqueous inflow or in the volume of blood in the uvea, and that presumably, in a case of closed-angle glaucoma giving a positive result, part of the rise in tension may be due to this factor as well as to closure of the angle of the anterior chamber.

Summary

A statistical analysis of the results of the darkroom test on a control series of 57 normal eyes and a test series of 108 eyes with closed-angle glaucoma is presented.

A positive result is regarded as a rise in ocular tension of more than 8.5 mm. Hg.

A positive result is more likely to occur where the initial tension is 25–30 mm. Hg than where it is below this figure, and similarly the magnitude of the resulting increase in tension is greatest when the initial tension level is 25–30 mm. Hg.

In early closed-angle glaucoma a negative result occurs more often than a positive one.

A small but definite rise in ocular tension occurs in normal eyes with the test.

The significance of these findings is discussed.

I wish to acknowledge the helpful criticism given by Sir Stewart Duke-Elder in the preparation of this paper.

I also wish to record my thanks to Mr. T. Tarrant of the Department of Medical Illustration, Institute of Ophthalmology, for the preparation of the line drawings.

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SOME OBSERVATIONS ON CHRONIC CLOSED-ANGLE GLAUCOMA*

BY

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AT WHAT stage in its course closed-angle glaucoma may be said to have become chronic is difficult to define. When, however, pathological cupping of the optic disc and visual field loss have occurred in an eye with closed-angle glaucoma, the disease may reasonably be said to have reached the chronic stage. The aqueous outflow in such an eye is usually regarded as being permanently impaired by the development of goniosynechiae. It is the purpose of this communication to show that, in some cases, this advanced stage of chronic closed-angle glaucoma may result from closure of the filtration angle by irido-corneal contact alone, without the development of either synechiae or permanent trabecular change.

Barkan (1938) has stated that contact between the root of the iris and the entrance to the angle will, if transient, result in a rise of pressure of short duration; if the contact be not soon relieved by medication or operation, permanent organic adhesions will result. Grant (1951) has shown that periods of transient closure of the angle are associated with periods of reduced outflow of aqueous.

It has already been suggested (Phillips, 1956) that, in cases of "subacute" closed-angle glaucoma, the uppermost part of the angle of the anterior chamber is closed by irido-corneal contact before any attacks of hypertension occur, and that the area so obstructed advances downwards nasally and temporally until a critical amount of angle remains open below, the lowermost limits of this obstruction varying from time to time depending on such factors as pupillary dilatation.

While closure of the angle in cases of subacute closed-angle glaucoma was being investigated by means of the darkroom-outflow test (Foulds, 1956), it was noted that in certain cases the facility of aqueous outflow, measured by tonography (Grant, 1951), was lower than normal at the start of the test, although the ocular tension was within the accepted limits of normality. Moreover, the facility of aqueous outflow could be further reduced by a period in the dark, or could be increased by the instillation of a miotic, indicating an obstruction to aqueous outflow of variable degree. The following example illustrates this.

Case 1, a male aged 63, had developed an acute hypertensive episode in the right eye early in 1954. The attack responded to miotic therapy and thereafter the patient had been instilling pilocarpine 2 per cent. twice daily into this eye. In June 1955, the vision in the

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right eye was 6/9 unaided and the visual field full. Gonioscopy revealed a "very narrow angle, closed above but just open below". The ocular tension was found to be 28 mm. Hg some 7 hours after the instillation of pilocarpine 2 per cent.; the facility of aqueous outflow was 0·10. One hour in the dark caused the ocular tension to rise to 34 mm. Hg while the facility of aqueous outflow fell to 0·05. Immediately after the instillation of pilocarpine 2 per cent. the ocular tension was found to be 28 mm. Hg but the facility of outflow had risen to 0·14. A further hour in the dark resulted in a rise of ocular tension to 30 mm. Hg and a fall in the facility of outflow to 0·08.

The results in this case suggested that, even on treatment with miotics, part of the angle of the anterior chamber was constantly obstructed by irido-corneal contact, the limits of which were variable; for most of the time the outflow of aqueous was as low as that found in cases of well-established chronic simple glaucoma. However, the fact that the facility of aqueous outflow immediately after the instillation of pilocarpine rose just to within normal limits suggested that some area of the angle was not permanently obstructed. The low outflow readings obtained at other times suggested that this type of case might eventually develop cupping of the optic disc and field loss without the appearance of permanent goniosynechiae.

Proof of this would be possible if the ocular tension in a well-developed case of chronic closed-angle glaucoma with advanced visual field loss and cupping of the optic disc could be relieved by a peripheral iridectomy and the angle of the anterior chamber subsequently shown to be open and free from goniosynechiae. A normal outflow factor post-operatively would indicate the absence of permanent trabecular change. Two cases of this type are described below:

Case 2, a male, aged 49, complained of attacks of blurred vision in the right eye for one year. He was found to have corneal oedema in the affected eye and an ocular tension of 60 mm. Hg (Schiötz) which was reduced by miotics to 48 mm. Hg. Gonioscopy revealed a very narrow angle apparently entirely closed. The optic disc was pathologically cupped and the visual field constricted to within 10° of the fixation point (Fig. 1).

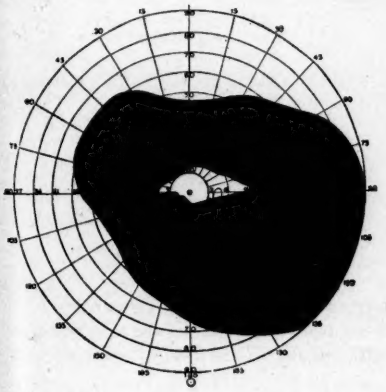

FIG. 1.—Field of vision of Case 2 before operation.

A peripheral iridectomy was performed, after which the angle of the anterior chamber could be seen to be open and free from goniosynechiae (Fig. 2). The ocular tension thereafter did not rise above 20 mm. Hg and the facility of aqueous outflow was 0·25.

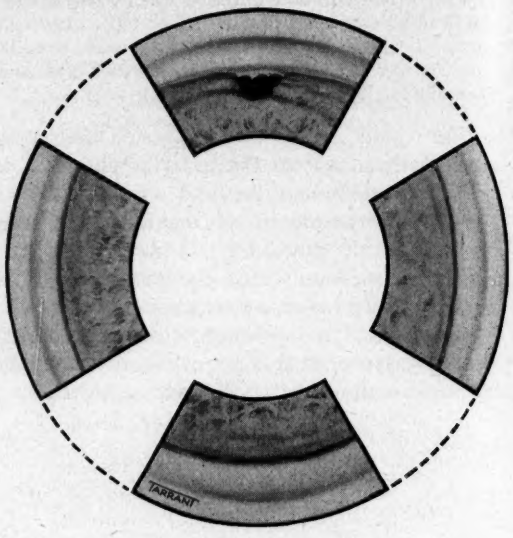

FIG. 2.—Post-operative gonioscopic appearance of the angle in Case 2. The angle is open in all sectors. The pre-operative appearance of the angle was similar to that in Case 3 (see Fig. 4).

Case 3, a male aged 72, complained of discomfort in the right eye and failing vision for nine months. The ocular tension was found to be 70 mm. Hg, reduced by miotics to between 30 and 40 mm. Hg. The optic disc was deeply cupped and the visual field showed nasal loss within 5° of the fixation point, together with a typical Bjerrum scotoma (Fig. 3).

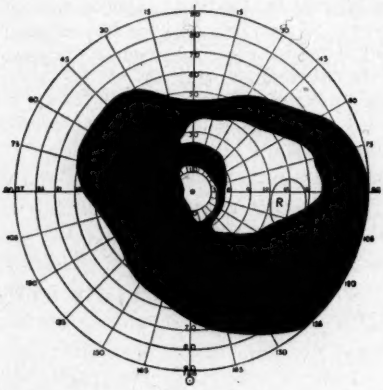

FIG. 3.—Field of vision of Case 3 before operation.

Gonioscopy shortly after the instillation of eserine 0·5 per cent. and pilocarpine 2 per cent. revealed a narrow angle, open in the lower segment but closed in the upper (Fig. 4, opposite). The facility of aqueous outflow at that time was 0·14 in the affected (compared with 0·20 in the unaffected) eye.

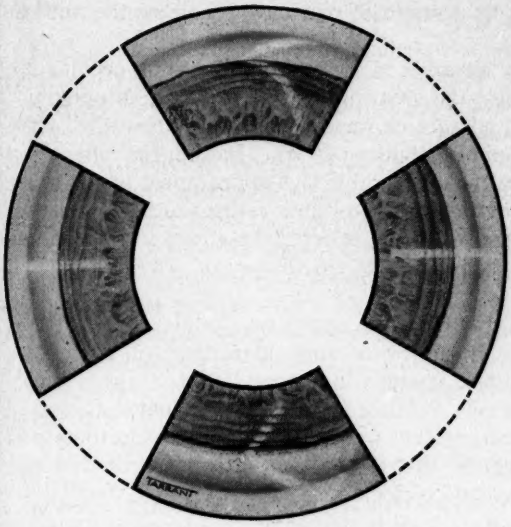

FIG. 4.—Gonioscopic appearance of the angle of the anterior chamber in Case 3 before operation. It is impossible to be certain whether the closure of the angle above is due to goniosynechiae or to irido-corneal contact.

A peripheral iridectomy was performed on the right eye, after which the previously closed sector of the angle could be seen to be open and free from goniosynechiae (Fig. 5). The ocular tension remained in the region of 20 mm. Hg while facility of aqueous outflow was 0·28.

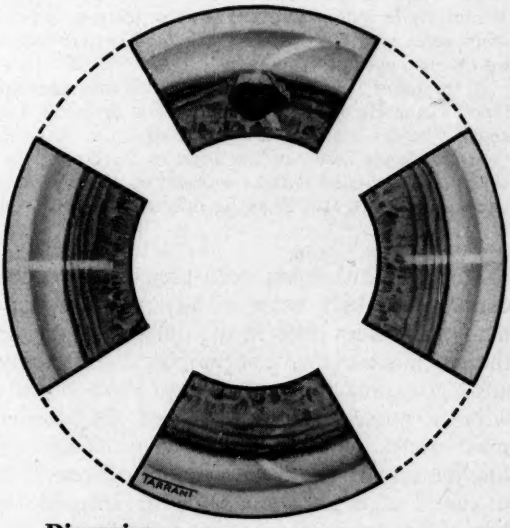

FIG. 5.—Gonioscopic appearance of the angle of the anterior chamber in Case 3 after a peripheral iridectomy had been performed. It is now obvious that the pre-operative closure of the angle was due to irido-corneal contact (see Fig. 4).

Discussion

The case histories described above show that chronic closed-angle glaucoma may be caused by *irido-corneal contact* extending so far round the angle

of the anterior chamber that no amount of miosis will increase the outflow of aqueous to normal.

In the angle of an anterior chamber of normal depth goniosynechiae are easily seen. In a narrow angle the great difficulty in differentiating goniosynechiae from irido-corneal contact or merely extreme narrowness of the angle has already been pointed out (Phillips, 1956). Indeed, the differential diagnosis must depend much less on the objective appearances of the angle than on the results of provocative tests, outflow estimations, response of tension to miotics, and the history of the patient: the absence of any acute hypertensive episodes and the shortness of the history of symptoms are of great importance.

Since the criteria for diagnosis are so imprecise, failure of peripheral iridectomy to cure a case of chronic closed-angle glaucoma will sometimes occur even if the history seems to favour irido-corneal contact as the cause. One such case is recorded below. Possible failure was anticipated as closure of the angle had probably been present for 3 years and the iridectomy was done at 10 o'clock (right eye) so that if necessary a subsequent drainage operation might be performed at 12 o'clock.

Case 4, a female aged 51, first attended hospital when aged 44 with a complaint of "haloes" in the right eye. The left was amblyopic (a concomitant convergent strabismus being present). Miotic therapy was advised. At the age of 48, the right eye, which had a visual acuity of 6/5 with correction, showed a tension which was only once below 30 mm. Hg in spite of miotics: all other tension readings were over 40 mm. Hg. Gonioscopy revealed a "very narrow" angle. The right field was full. Operation was advised for the right eye but was refused.

By the age of 51, the right eye showed definite supero-nasal field loss, a tension never less than 32 mm. Hg even after strong miotic drops, an angle blocked from 10 to 4 o'clock and a "border-line" outflow factor of 0·12. A peripheral iridectomy converted the "narrow" lower sector of the angle to "medium", no change appearing in the upper which must therefore have been closed by goniosynechiae. The tension remained raised and the outflow 0·12. Drainage operation was subsequently performed.

This publication has been prepared in order to prove that irido-corneal contact may be a cause of advanced chronic closed-angle glaucoma. So many difficulties arise in the differential diagnosis of goniosynechiae when the angle is narrow, that peripheral iridectomy in cases of chronic closed-angle glaucoma apparently due to irido-corneal contact, should be used only with the greatest caution. Indeed, the possibility of its failure even in the most carefully chosen case of chronic closed-angle glaucoma serves to underline the importance of performing peripheral iridectomy in the *early* stages of closed-angle glaucoma *before* the chronic stage is reached. On the other hand, if a drainage operation is performed on all cases of chronic closed-angle glaucoma, some eyes will be subjected to an unnecessarily major procedure.

Summary

Evidence has been presented to show that advanced chronic closed-angle glaucoma with field loss and cupping of the optic disc may be caused not only by goniosynechiae, but also by irido-corneal contact.

Successful treatment of the latter is possible by peripheral iridectomy, whereas a drainage operation is required for the former. Gonioscopic discrimination between irido-corneal contact and goniosynechiae in a narrow angle is impossible, so that more reliance must be placed on the liability of tension and outflow in response to miotics, the absence of previous acute hypertensive episodes, and the shortness of the history of symptoms, in diagnosing the type due to irido-corneal contact. The existence of this diagnostic problem, which is sometimes insoluble, underlines the importance of discovering cases of closed-angle glaucoma long before chronicity becomes established, *i.e.* in the stage when peripheral iridectomy is almost certain to be curative.

We gratefully acknowledge the helpful criticism given by Sir Stewart Duke-Elder in the preparation of this paper.

The clinical details of patients have been made available for publication by kind permission of Mr. D. P. Greaves, Mr. S. J. H. Miller, and Mr. J. G. Milner. We wish to record thanks to Mr. T. Tarrant of the Department of Medical Illustration, Institute of Ophthalmology, for his preparation of the drawings.

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NATURAL HISTORY OF ONCHOCERCIASIS*

BY

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Since the first description of ocular onchocerciasis in Africa was published (Hissette, 1931) many records have been made of the ocular lesions (*e.g.* Bryant, 1935; Hissette, 1938; Toulant and Boithias, 1952a, 1952b, 1954; World Health Organization Regional Conference on Onchocerciasis, 1956). However, no detailed account has been written of the progress of ocular signs and visual acuity in an untreated community, nor has any serious attempt been made to study the prognosis of ocular lesions in onchocerciasis. The need for such assessment is indicated by recent estimates that the disease is the cause of blindness in 10,000 persons in the Northern Territories of the Gold Coast (Waddy, 1956) and 20,000 persons in Northern Nigeria (Budden, 1956) and by the discovery of increasing numbers of Europeans suffering from early ocular lesions acquired in these territories.

Recently an investigation was completed in which a record was made of the changes in visual acuity which occurred during a few years in a village community. In this paper these changes are related to the age, intensity of infection, distribution of microfilariae, and changes in ocular signs. Moreover, an attempt is made to classify the patients seen in Nigeria with a view to providing some guide to prognosis and some indication of which patients require treatment to prevent serious loss of vision.

Progress of Ocular Lesions

Method of Investigation

The village chosen, Bulki, one of the most heavily infected in N. Nigeria, was first examined in September, 1952, when 117 persons were seen. Of these 28 were under 10 years of age and, although thirteen of them had positive skin snips, visual acuity could not always be recorded and a full ocular examination was not always possible. This age group was therefore excluded from the analysis. Bulki was last visited in May, 1956, when of the original series of patients aged 10 years and over, ten were said to be dead, six young women to have married and moved to other villages, and one young man to have moved away. A further three persons were excluded

* Received for publication December 20, 1956.

because ocular diseases other than onchocerciasis confused the picture. The analysis was limited to the remaining 69 persons.

First Examination (September, 1952).—A skin snip was taken from the left iliac crest and the number of microfilariae per microscope field was recorded by the technique previously described (Budden, 1955). Visual acuity was recorded using an illiterate E test and ability to count fingers at distances up to 6 m. Ocular examination, using focal illumination, loupe, slit lamp, and electric ophthalmoscope, was carried out in a darkened hut.

Second Examination (September, 1953, *i.e.* 12 months after the first examination).—Only 21 of the 69 persons included in this analysis were re-examined. In these persons the density of microfilariae per mg. of tissue was determined as described by Kershaw, Duke, and Budden (1954). Samples were taken from the skin of the calf, deltoid, and outer canthus, and also from the conjunctiva.

Third and Final Examination (May, 1956, *i.e.* 43 months after the first examination).—The method used was the same as at the first visit.

Patient's Age.—This was estimated from the general appearance. The ages quoted in this paper are those at the first visit in 1952.

Changes in Visual Acuity.—Changes of one division (*e.g.* 6/6 to 6/9, 6/18 to 6/12, or "Hand Movements" to "Perception of Light") were regarded as too small to be reliable and were not recorded as either an improvement or a deterioration.

Findings at Bulki

(1) Incidence and Density of Infection.—The community as a whole was heavily infected. No person over the age of 19 years had a negative skin snip from the lower half of the body at any visit and only two persons, both female, of the twelve in the 10 to 19 year age group had negative snips. The density of microfilariae in the skin tended to rise with age, *i.e.* with length of exposure to infection, up to and including the 30 to 39 year age group. Over the age of 40 years however, the density of microfilariae tended to fall, more particularly in the legs.

(2) Incidence of Ocular Lesions and Reduced Vision at First Examination.—(Table I).—In the 10 to 19 year age group, although microfilariae were present in the anterior chamber of five out of 26 eyes, no loss of visual acuity was found. Visual loss and blindness occurred in the 20 to 29 year age group, and the incidence increased with age until, in persons over the age of 40 years, visual acuity was less than 6/9 in 54 per cent. of eyes, and 29 per cent. of eyes were blind.

(3) Ocular Changes.—During the interval of 43 months between the first and last examination the changes in visual acuity occurred which are recorded in Table I (overleaf).

TABL
CHANGES IN VISUAL ACUITY A ULKI IN

Age Group (yrs)	Total No. of Eyes	November, 1952									
		Eyes with Visual Acuity of:									
		6/6–6/9		6/12–6/24		6/36–C.F. 4		Blind		6/6–6/9	
		No.	Percent.	No.	Percent.	No.	Percent.	No.	Percent	No.	Perce
10+	26	26	100	0	0	0	0	0	0	26	100
20+	56	51	91	3	5	0	0	2	4	49	87
30+	28	15	54	7	25	4	14	2	7	16	57
40+	28	13	46	6	21	1	4	8	29	17	61
All Ages	138	105	76	16	12	5	4	12*	9	107	78

C.F.4 = Ability to count fingers at 4 m.

This figure u

Loss of Vision.—It will be noticed that, although no loss of vision occurred in the 10 to 19 year age group, deterioration in vision occurred in some eyes in all the later age groups, and was most frequent (21 per cent. of all eyes) in persons aged 30 to 39 years.

The most severe loss of vision occurred in four eyes which developed glaucoma secondary to iridocyclitis (1952: 6/12, 6/9, 6/6, 6/6; 1956: perception of light, hand movements, hand movements, hand movements). With the development of other lesions, the deterioration in visual acuity was usually less dramatic, whether loss of vision was considered to be due to anterior segment lesions (1952: counting fingers at 4 m., 6/18, 6/18, 6/12, 6/6; 1956: no perception of light, hand movements, 6/60, counting fingers at 2 m., 6/18) or choroido-retinal degeneration (1952: counting fingers at 1 m., 6/36, 6/24, 6/6; 1956: perception of light, perception of light, counting fingers at 5 m., perception of light).

Improvement in Vision.—This occurred in a small proportion of eyes in the 30 to 39 year age group (vision improved in two out of thirteen eyes: 1952: 6/12, 6/12; 1956: 6/6, 6/6) and in a larger proportion of eyes in the 40+ age group (vision improved in five out of fifteen eyes: 1952: 6/36, 6/18, 6/18, 6/12, 6/12; 1956: 6/9, 6/9, 6/6, 6/6, 6/6). Improvement in visual acuity was found only in patients with anterior segment lesions and was usually associated with the disappearance of microfilariae from the anterior chamber and the disappearance of the signs of active inflammation, *i.e.*, fluffy corneal opacities and active iridocyclitis).

(4) Association between Intensity of Head Infection and Progress or Regress of Ocular Lesions.—Table II (overleaf) relates the density of microfilariae found in skin snips taken from various parts of the body in September, 1953, to the ocular findings in September, 1952, and May, 1956. It is apparent that relatively heavy infection, particularly in the head region, and persistence of microfilariae in the anterior chamber is usually associated with the progress of anterior segment lesions and loss of visual acuity. Conversely, relatively light infection was associated with improvement in visual acuity or, in persons

TABL
CUITY A ULKI IN RELATION TO AGE

Blind	May, 1956								Difference					
	Eyes with Visual Acuity of:								Eyes in which Visual Acuity:					
	6/6–6/9		6/12–6/24		6/36–C.F. 4		Blind		Remained Constant		Improved		Deteriorated	
Percent	No.	Percent.	No.	Percent.	No.	Percent.	No.	Percent.	No.	Percent.	No.	Percent.	No.	Percent.
0	26	100	0	0	0	0	0	0	26	100	0	0	0	0
4	99	87	1	2	0	0	6	11	50	89	0	0	6	11
7	76	57	2	7	3	11	7	25	20	71	2	7	6	21
29	37	61	2	7	1	4	8	29	22	79	5	18	1	4
9	237	78	5	4	4	3	21	15	116	84	7	5	13	11

This figure underestimates the incidence of blindness found at the first visit because several blind persons died before the final visit.

with normal vision at the first examination, with no deterioration. This was particularly obvious when microfilariae were absent from the anterior chamber or, when present at the first visit, disappeared before the final examination.

A Suggested Method of Classifying Onchocercal Infections in Africa

Clinical experience in the examination of over 1,600 cases of onchocerciasis, more than 500 of which had ocular lesions, has suggested that patients in whom the microfilariae of *O. volvulus* can be demonstrated may be divided into three types, which, as is shown in the discussion, are believed to be stages in the progress of the disease. To illustrate these three stages and to record their incidence and age distribution, persons were examined in two Northern Nigerian villages: Bulki with a standardized infection rate of 754, and therefore one of the most heavily infected villages in N. Nigeria, and Mbilla, a typical moderately infected village. Since women tend to be more lightly infected than men, and the development of the three stages takes place more slowly in females, the analysis was confined to men. At each village the analysis was limited to 36 males with the following age distribution:

5 to 9 years, five persons
10 to 19 years, seven persons
20 to 29 years, nine persons
30 to 39 years, five persons
40 to 49 years, five persons
50+ years, five persons.

Stage I. Light Infection Regionally Localized

Microfilariae in relatively small numbers are found in one region of the body, not necessarily the lower limbs; a subcutaneous nodule may be present in the same quarter, and pruritis and papular eruption may also be more intense in the same region.

TABL

CHANGES IN VISUAL ACUITY AND OCULAR SIGNS IN RELATIO THE

Changes in Visual Acuity	Sex	Age (yrs)	SEPTEMBER, 1952					Density
			Visual Acuity		Microfilariae in Anterior Chamber		Ocular Signs	Calf
			Right	Left	Right	Left		
Improvement (5)	F	30+	6/9	6/12	–	+	Left fluffy corneal opacities	7
	M	30+	6/12	6/9	++	+	Bilateral iritis	60
	M	40+	6/18	6/12	++	–	Bilateral fluffy corneal opacities	7
	M	40+	6/9	6/12	+	–	Bilateral fluffy corneal opacities	40
	M	50+	6/18	6/36	+	–	Bilateral fluffy corneal opacities Iridocyclitis	50
							Mean	33 S.D. 22
Deterioration (6)	M	20+	H.M.	C.F. 1	++	+	Fluffy corneal opacities Iridocyclitis Advanced choroidoretinal degeneration	110
	M	20+	6/9	6/12	++	++	Fluffy corneal opacities Pigment deposits on lens and cornea Early choroidoretinal degeneration	100
	M	20+	6/12	6/5	+++	++	Active iritis with flare	90
	M	30+	C.F. 4	6/12	?	++	Bilateral iridocyclitis Right glaucoma and corneal epithelial oedema	220
	F	30+	6/36	6/18	+	+	Iridocyclitis Early choroidoretinal degeneration	7
	M	40+	6/5	6/5	–	–	No signs	110
							Mean	106 S.D. 62
Normal at First Visit and No Deterioration (8)	F	10+	6/6	6/6	–	–	No signs	0
	M	10+	6/5	6/5	–	+	Bilateral fluffy corneal opacities	9
	M	10+	6/5	6/5	++	++	Fluffy corneal opacities Pigment deposits on lens and cornea	16
	M	10+	6/5	6/5	–	+	No signs	20
	M	10+	6/5	6/5	–	–	No signs	45
	M	10+	6/5	6/5	–	–	No signs	8
	M	20+	6/6	6/5	++	++	Scanty bilateral fluffy corneal opacities	50
	M	40+	6/6	6/6	–	–	No signs	20
							Mean	21 S.D. 15
Blind at First Visit and No Improvement (2)	M	40+	N.P.L.	P.L.	?	?	Bilateral glaucoma Right superficial corneal epithelial oedema	100
	M	50+	P.L.	P.L.	+	–	Advanced iritis Choroidoretinal degeneration	20

C.F.4 = Ability to count fingers at 4 m. H.M. = Ability to see hand movements.

TABLE 10 THE DENSITY AND DISTRIBUTION OF MICROFILARIAE

SEPTEMBER, 1953				MAY, 1956				
Density of Microfilariae per mg.				Visual Acuity		Microfilariae in Anterior Chamber		Ocular Signs
Calf	Deltoid	Outer Canthus	Conjunctiva	Right	Left	Right	Left	
7	5	2	0	6/6	6/6	–	–	No apparent change
60	18	1	0	6/6	6/6	–	–	Posterior synechiae
7	1	1	0	6/6	6/6	–	–	No signs
40	3	2	1	6/6	6/6	+	–	Bilateral fluffy corneal opacities Early tongues
50	60	2	4	6/9	6/9	–	–	Corneal opacities and pigment deposits less
33 S.D. 22	17 S.D. 22	1·6 S.D. 0·5	1·0 S.D. 1·5					
110	43	6	18	P.L.	P.L.	+ + +	+ +	No apparent change
100	30	3	3	H.M.	P.L.	?	?	Glaucoma Bilateral corneal epithelial oedema
90	65	6	3	C.F. 2	6/18	+	+	Posterior synechiae Choroidoretinal degeneration
220	55	6	5	N.P.L.	6/18	?	+ +	Right corneal degeneration Left choroidoretinal degeneration
7	15	2	8	P.L.	6/12	+	+	Choroidoretinal degeneration more advanced
110	100	2	3	6/6	6/9	+	+	Fluffy opacities Early left choroidoretinal degeneration
106 S.D. 62	51 S.D. 27	4·1 S.D. 1·9	6·6 S.D. 5·4					
0	1	1	0	6/6	6/6	–	–	No signs
9	7	2	0	6/6	6/6	–	+	Bilateral fluffy corneal opacities more numerous
16	5	2	4	6/6	6/6	+ +	+ + +	No change except tongues of corneal opacity developed
20	12	1	1	6/5	6/5	–	–	No signs
45	5	1	0	6/5	6/5	–	+	No signs
8	4	0	0	6/5	6/5	–	–	Bilateral fluffy corneal opacities
50	2	1	0	6/6	6/5	–	–	Scanty fluffy corneal opacities right eye only
20	5	1	1	6/6	6/6	–	–	No signs
21 S.D. 15	5·1 S.D. 3·1	1·1 S.D. 1·7	0·7 S.D. 1·3					
100	40	1	2	N.P.L.	N.P.L.	?	?	Bilateral glaucoma Bilateral superficial corneal epithelial oedema
20	110	10	4	N.P.L.	N.P.L.	–	–	No apparent change

P.L. = Perception of light. N.P.L. = No perception of light.

Ocular Lesions.—These are uncommon. Microfilariae only occur in the head region in a small proportion of persons, and even if the organisms do invade the anterior segment of the eye, their numbers are small and ocular lesions may or may not occur. Symptoms when present are mild conjunctival irritation and photophobia. The signs are slight injection and oedema of the conjunctiva, slightly increased lacrimation, and moderate numbers of fluffy corneal opacities. The opacities lie in the superficial layers of the substantia propria and are usually situated near the limbus in the interpalpebral area. These corneal lesions appear to start as a fluffy longitudinal opacity around a dead microfilaria, but when fully developed they are disc-shaped and about 0·5 mm. in diameter. They were well described at the World Health Organization Conference on African Onchocerciasis in October, 1954, by Dr. A. J. Boase (Specialist Ophthalmologist, Uganda) as having the appearance of cracked ice. They slowly resolve over a period of about 3 months after the disappearance of microfilariae from the eye. The term "fluffy" is preferred to the term "nummular" (Ridley, 1945), to distinguish the lesions characteristic of active ocular onchocerciases from the homogeneous disc-shaped corneal opacities commonly seen in Nigeria in persons who have never been exposed to onchocerciasis.

Very fine brown pigment deposits on the posterior surface of the cornea and anterior surface of the lens may be seen in the heavier African infections. No other ocular lesions were seen at this stage. Visual acuity is usually normal.

Stage II. Generalized Infection

The intensity of infection is heavy and generalized. The concentration of microfilariae is highest in the lower limbs, but the organisms are also present in the head region and may invade the eyes, where they are seen in conjunctival snips, motile in the anterior chamber, adherent to the posterior surface of the cornea, or lying immobile in the substantia propria. Lichenification, which is most marked on the skin of the lower limbs, also appears on the upper trunk, upper limbs, and head. Nodules tend to be present in larger numbers than in Stage I.

Ocular Lesions.—When invasion of the anterior segment of the eye is small the reaction is the same as in Stage I. When invasion is heavy, patients complain of ocular pain, photophobia, and blurred vision. Slight oedema of the lids may occur. The conjunctiva is slightly oedematous and slightly injected, particularly near the limbus, and mild ciliary injection may be present. Small inflammatory swellings resembling phlyctens may develop in the conjunctiva.

The cornea contains fluffy opacities similar to those seen in Stage I, but they may be present in larger numbers and be scattered over the whole interpalpebral area. What appear to be microfilariae may be seen as opaque, motionless, corrugated threads in the substantia propria—a motile microfilaria such as described by Ridley (1945) has not been seen. At a later stage in heavy infections the fluffy opacities appear to coalesce, forming an area of superficial corneal opacity, often with some pigmentation, spreading into the cornea like tongues at 4 o'clock and 8 o'clock. The opacity spreads around the cornea adjoining the

lower half of the limbus and eventually invades the pupillary area. Degenerative changes may occur in this opaque area.

Fine pigment deposits occur on the posterior surface of the cornea and anterior surface of the lens. They tend to be more numerous than in Stage I and may coalesce to form larger irregular pigment deposits. Posterior synechiae may develop and secondary glaucoma is not uncommon. Signs of active iridocyclitis, *i.e.* true keratitis punctata, flare, and cells in the anterior chamber are rarely seen and then only in heavily infected patients. The pear-shaped pupil, drawn down towards an opaque mass at the base of the anterior chamber has been seen only rarely (nine cases).

After long-standing intense ocular infection the iris appears smooth, atrophic, and slightly depigmented. The lens capsule may exfoliate. True secondary cataract, as distinct from coincident senile cataract, is uncommon and only occurs in very heavy infections.

Choroido-retinal degeneration may be seen in long-standing infections of this type. The most usual changes are a widespread gross tigroid appearance, presumably due to thinning of the retina, and aggregations of superficial retinal pigment which may be of very varied size and shape. The retinal blood vessels are often narrowed and may be sheathed for up to two disc diameters beyond the disc, and the nervehead atrophies. Large patches of choroidal sclerosis may be seen in advanced cases. These changes have been described in detail by Hissette (1931 and 1938), Bryant (1935), Ridley (1945), and Toulant and Boithias (1954).

Active papillitis was seen in a small number of patients.

Stage III. Regression

The concentration of microfilariae in the skin is less than in Stage II, and if microfilariae are present in the head region they occur only in small numbers unsupported by a high concentration in the lower part of the body. Lichenification of the skin tends to be replaced by atrophic changes, *i.e.* "a crushed tissue paper" appearance over most of the body, together with, in some previously heavy infections, smooth atrophic skin with mottled white patches overlying the shins. Nodules tend to be present in still larger numbers than in Stage II.

Ocular Lesions.—Microfilariae are not seen in the anterior segment of the eye and no active inflammatory reaction occurs. Opaque corneal infiltration, pigment deposits, posterior synechiae, and glaucoma produced by previous inflammation are present in many eyes. Choroido-retinal degeneration and optic atrophy also occur.

In addition to these three stages in which microfilariae are found, there is an incubation period lasting about 15 to 18 months before microfilariae are demonstrable in the skin or eye. Moreover, a late stage of burnt-out infection sometimes occurs in elderly persons in whom typical dermal and sometimes ocular lesions are present, but in whom microfilariae are not found.

Distribution of the Different Stages of Onchocercal Infection and of Ocular Lesions amongst Persons living in Areas of Heavy, Moderate, and Light Endemicity and amongst Persons exposed to Occasional Infection only

(1) Heavy Endemic Areas (Standardized infection rate, as determined by a single skin snip from the left iliac crest, more than 501 per 1,000 persons of all ages).—The intensity of infection in individual persons is usually heavy. Stage I occurs early in life and most persons are suffering from Stage II infection. Stage III is uncommon but may be seen in elderly persons. The data for Bulki, one of the most heavily infected villages in N. Nigeria, are given in the Figure (opposite).

Massive and prolonged invasion of the anterior segment of the eye by microfilariae in Stage II leads to severe lesions, *i.e.* opaque corneal infiltration and iridocyclitis. This is the major cause of visual loss, though choroido-retinal degeneration is also common (Budden, 1955).

(2) Moderate Endemic Areas (Standardized infection rate 251–500 per 1,000 persons of all ages).—The intensity of infection in individual persons is usually moderate. Stage I infection appears in the second and third decades of life, Stage II is most common in the fourth decade, and Stage III in the fifth and sixth decades. Data for Mbilla, a typical village of this type, are given in the Figure (opposite).

The major cause of reduced vision is choroido-retinal degeneration, but as the anterior segment of the eye is invaded by moderate numbers of microfilariae in Stage II infections the resultant iridocyclitis is almost as important a cause of visual loss (Budden, 1955).

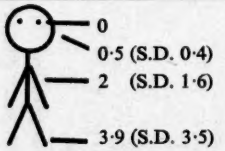
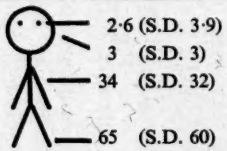
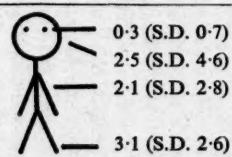
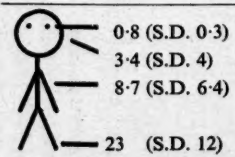
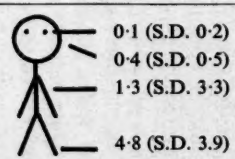
(3) Light Endemic Areas (Standardized infection rate 0–250 per 1,000 persons of all ages).—The intensity of infection in individual persons is usually light. Stage I infection is seen in all age groups, but Stage III predominates in persons over the age of 50 years. Stage II infection is uncommon and in some of the most lightly infected villages has never been seen. When it occurs the number of microfilariae entering the eye is so small that iridocyclitis, the only permanent lesion of the anterior segment, is infrequent.

Visual loss is uncommon and is usually due to choroido-retinal degeneration in the later years of life (Budden, 1955).

(4) Persons exposed to Occasional Infection (Expatriates and Africans normally living in non-endemic areas).—Stage I infection is common. A European with Stage I infection involving the eyes was described by Ridley and Anderson (1950), and two other European patients, probably at this stage of infection but with no eye involvement, were described by Chartres (1955).

Microfilariae invade the anterior segment in small numbers in Stage I, producing a few transient fluffy opacities and sometimes, in Africans,

CONCENTRATION AND DISTRIBUTION OF MICROFILARIA OF *O. VOLVULUS* AT EACH STAGE OF INFECTION AMONGST MALES LIVING IN VILLAGES WITH HEAVY AND MODERATE INCIDENCE OF INFECTION

Stage		I	II	III	Not Infected
BULKI (Heavily Infected)	Percentage of Anterior Chambers containing Microfilariae	0 per cent	68 per cent	0 per cent	0 per cent
	Density of Microfilariae	 0 0·5 (S.D. 0·4) 2 (S.D. 1·6) 3·9 (S.D. 3·5)	 2·6 (S.D. 3·9) 3 (S.D. 3) 34 (S.D. 32) 65 (S.D. 60)		
	Mean Age (yrs)	9 (S.D. 3)	30 (S.D. 19)		7
	No. of Persons	5	30	0	1
MBILLA (Moderately Infected)	Percentage of Anterior Chambers containing Microfilariae	6 per cent	43 per cent	0 per cent	0 per cent
	Density of Microfilariae	 0·3 (S.D. 0·7) 2·5 (S.D. 4·6) 2·1 (S.D. 2·8) 3·1 (S.D. 2·6)	 0·8 (S.D. 0·3) 3·4 (S.D. 4) 8·7 (S.D. 6·4) 23 (S.D. 12)	 0·1 (S.D. 0·2) 0·4 (S.D. 0·5) 1·3 (S.D. 3·3) 4·8 (S.D. 3.9)	
	Mean Age (yrs)	23 (S.D. 2·6)	36 (S.D. 14)	47 (S.D. 11)	17 (S.D. 29)
	No. of Persons	9	7	8	12

At both villages 36 males with the same age distribution (see text) were examined.
The concentration is recorded as the number of microfilariae per mg. of conjunctival tissue, and of skin from outer canthus, deltoid, and calf.

deposits of fine pigment on the posterior surface of the cornea and anterior surface of the lens. No active iridocyclitis, opaque corneal infiltration, or choroido-retinal lesion has been seen by the author in this type of patient.

Discussion

(1) Classification of Onchocercal Infection

It is believed that the types of onchocercal infection described are in fact stages in the progress of the disease in a person living in an endemic area and therefore, presumably, exposed to repeated infection up to the time of examination. This is suggested by the fact that, at both villages investigated, the mean age of the patients rises progressively from Stage I to Stage III (Figure). Moreover, at Bulki, where it was possible to re-examine patients after an interval, some patients who were at one stage at the first visit had progressed to the next stage before the final visit.

The occurrence of Stage II depends on the building up of a heavy parasitic infestation in the definitive host; it has not been seen in persons visiting endemic areas, and it is uncommon in natives of lightly endemic areas.

(2) Pathogenesis of Ocular Lesions

Ocular lesions are related to the stage and intensity of infection:

Anterior Segment Lesions.—Previous investigation showed that the development of anterior segment lesions (keratitis involving the pupillary area and iridocyclitis) was associated with intense infection and the invasion of the anterior segment of the eye by microfilariae (Budden, 1955). Bulki is a heavily infected community and lesions of the anterior segment therefore dominate the ocular picture. The present findings clearly demonstrate that the progress of these lesions is associated with the presence of microfilariae in the anterior chamber supported by a heavy concentration of microfilariae in the head region. They also show that these lesions do not develop, or that they regress if present at an early stage, when microfilarae in the anterior chamber are absent or few, and are only supported by a low concentration of microfilariae in the head region.

It is apparent not only that these lesions are dependent on the invasion of the anterior segment by microfilariae but that the type of lesion developing depends on the intensity of this invasion. Microfilariae may invade the anterior chamber without signs developing; fluffy corneal opacities, pigment deposits on the posterior surface of the cornea and anterior surface of the lens, posterior synechiae and opaque corneal infiltration tend to occur in that sequence as the intensity of microfilariae in the anterior chamber rises.

There are two opportunities for microfilariae to invade the anterior segment of the eye and produce these lesions—in Stages I and II. Thus the fluffy corneal opacities, and in Africans pigment deposits, which develop in Stage I are liable to occur in expatriates or in Africans visiting endemic areas, as well as in natives of endemic areas. In the latter group this stage tends to be seen at an earlier age as the endemicity rises. The more serious lesions, leading to a permanent loss of vision, appear to develop only as a result of Stage II infection. In natives of

lightly infected areas this invasion of the anterior segment is rare and the intensity of invasion is low; thus pigment deposits and posterior synechiae are the only permanent lesions to develop. In natives of heavily endemic areas, on the other hand, Stage II infection develops at a relatively early age and the intensity of microfilariae in the anterior segment at this stage is so heavy that all types of anterior segment lesion are liable to occur.

Posterior Segment Lesions.—Choroido-retinal lesions have not been seen by the author in very lightly infected persons (*e.g.* in Europeans who have only been exposed intermittently). Choroido-retinal lesions occur in natives of all endemic areas including the most lightly infected villages where Stage II has never been seen. The incidence of these lesions increases and the average age of onset falls as the intensity of infection in the community rises. There is still some doubt how onchocercal infection produces these lesions, although it has been suggested (Budden, 1955) that they are unlikely to be due to the invasion of the eye by microfilariae along the same route as that which causes anterior segment lesions and that they may possibly result from a circulating toxin.

In conclusion, I would stress that our present knowledge is fragmentary. For instance, it is not known why microfilariae concentrate in the lower part of the body in Stage II, although it would appear that this distribution assists the uptake of microfilariae by *S. damnosum*, which in Nigeria bite almost exclusively on the legs (Crosskey, 1955). It is not known why, at a later stage in the disease, microfilariae are always found in the head region (Stage II), although this spread appears to be related to an increase in the concentration of microfilariae in the body as a whole. It is not known why the concentration of microfilariae in the skin and in the eyes falls in the later stages of the disease (Stage III) whilst the patient is still presumably exposed to infection, although this may be related to a different mode of life in old age, increased resistance on the part of the host, or anatomical changes in the skin excited by the prolonged presence of microfilariae (see Jamison, Kershaw, Duke, and Fejer, 1955). Although it has been possible to study the progress of the disease in natives of endemic areas, I have little information about the progress of infection acquired during exposure for a limited period. However, it seems likely that, although mild onchocerciasis has only recently been diagnosed amongst Europeans serving in West Africa, it previously existed and that, although no treatment was given, the consequences were not sufficiently serious to attract attention. Although these gaps in our knowledge remain, the study of the incidence of the ocular lesions in different communities and the relationship of these lesions to the concentration and distribution of microfilariae in the body as a whole has thrown some light on the natural history of ocular onchocerciasis, and provided some guide to prognosis and treatment.

(3) Prognosis

Consideration of the stage and intensity of infection together with age and

likelihood of re-infection provides a basis on which an assessment can be made of the risk of ocular lesions developing, or of the progress or regress to be expected in existing lesions.

Anterior Segment Lesions.—Slight conjunctival irritation, conjunctival inflammation, and fluffy corneal opacities may develop in any person in whom microfilariae enter the anterior part of the eye even in small numbers, *i.e. in Stage I involving the* head region or in light Stage II infection. However, these lesions do not always follow invasion of the eye by microfilariae and if they develop they resolve later. No permanent loss of vision is to be expected unless a more heavy invasion occurs. Heavy invasion of the anterior segment by microfilariae is liable to occur at Stage II in natives of moderately or heavily endemic areas, and the risk can be assessed in the individual from the concentration of microfilariae in the skin and anterior chamber. The severity of the lesions to be expected increases with the concentration of microfilariae in the body particularly in the head region.

Posterior Segment Lesions.—The risk of developing these lesions increases with the intensity and duration of infection in the individual. No improvement in visual acuity or visual fields can be expected except in acute papillitis.

In the past, failure to appreciate the widely different ocular prognosis in different stages and intensities of infection has led to considerable confusion and unnecessary anxiety, particularly among laymen. There is an unfortunate tendency for them to use the term "river blindness" as synonymous with onchocerciasis in infections which would be more accurately described by some such term as "river itch".

(4) Therapy

Consideration of the way in which the stage and intensity of infection affect ocular prognosis helps to determine what treatment, if any, is indicated to protect the eyes.

Individual Patients.—Before embarking on treatment with filaricides in an attempt to prevent visual loss, the risk of such loss should be balanced against the discomfort and risk of treatment. For instance, although treatment with filaricides may be indicated in Stage I for other reasons, it is doubtful whether it is ever required at this stage to prevent loss of vision; at the other extreme, treatment is urgently required in heavy Stage III infections.

Mass Treatment.—In villages such as Bulki where 27 per cent. of the population over 30 years of age is blind one may be justified in attempting heroic measures in an attempt to control the progress of the disease. In the present state of our knowledge it is probably advisable to limit treatment to the younger age groups since it is here that prevention will be most effective and reactions to the destruction of the filariae least severe.

SUMMARY

The changes occurring in the eyes of a village community exposed to heavy endemic onchocerciasis over a period of 43 months are recorded.

Although visual deterioration was common, spontaneous improvement in ocular lesions and visual acuity occurred in a small proportion of persons.

The ocular changes are related to the concentration and distribution of microfilariae in the body.

Three stages in the progress of human infection with onchocerciasis which have been observed in Nigeria are described and the ocular lesions liable to occur at each stage are noted.

The prognosis of ocular onchocerciasis and its application to therapy are discussed in relation to the stage and intensity of infection.

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CAVERNOUS SINUS THROMBOPHLEBITIS*

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SEPTIC thrombosis of the cavernous sinus was first described with autopsy findings by Duncan (1821), and the classical description of the clinical signs was made by Bright (1831). Grove (1936), in a review of 400 cases, estimated that the mortality rate of the condition was practically 100 per cent., and Dixon (1926) remarked that reported recoveries were probably errors in diagnosis. With the development of chemotherapy and antibiotics, however, not only has this state of affairs greatly altered, but the condition itself seems to be becoming less frequent, since only four cases have been reported in Great Britain in the past 10 years (Young, 1946; McAllen and Shaw, 1952; Bennett, 1954; Haas, 1955). Of the three further papers published during this time, two refer to cases occurring before 1946 (Reid and McGuckin, 1956; Gregory, 1946), and one was written from Hungary (Miklós, 1950). The rarity of the condition to-day is presumably due to early treatment of facial sepsis with antibiotics. Even so, the death rate is still by no means negligible, and the ever increasing incidence of penicillin-resistant staphylococci, recently estimated at 37 per cent. for out-patients and 57 per cent. for in-patients (Fairbrother, 1956), will add to this. This paper presents two such cases in which the infection followed the development of a stye, one of which proved fatal.

Case Reports

Case 1, a woman aged 24, the mother of three children, was admitted to St. Thomas's Hospital on March 14, 1956; 4 days before admission she had complained of some irritation in the right eye without swelling or redness, and 2 days later there was an obvious stye on the lower lid near the inner canthus. Next day the eye was swollen and she was given 600,000 units of a long-acting form of penicillin by injection and 500,000 units in tablets by mouth. That evening she complained of headache. On the morning of the day of admission the eye was extremely swollen and she felt ill. It was thought that this might be an allergic reaction to penicillin and she was given 500 mg. tetracycline. At 2 p.m. the left eye began to swell, and her husband later described it as "going up as I watched". An hour later she was drowsy and disorientated, and on admission at 5 p.m. she was unconscious.

Examination.—She was comatose with marked meningism, and reacted only to painful stimuli by purposeless movements and a high-pitched cry. Temperature (axilla) 104·8° F., pulse irregular 92/min., respirations 18/min. (Fig. 1, opposite). There was severe bilateral proptosis and chemosis, the lids being so oedematous that it was only possible to force them apart by 1 or 2 mm., while between them the oedematous conjunctiva pouted forth. There were signs of a resolving stye on the right lower lid and the surrounding skin was hot and red. The oedema extended across the upper part of the face and temples, and there was a small oedematous area over each mastoid process. The pupils were only visible in part, but were central and reacted to light. No clear view of the fundi was obtained because of oedema and mistiness of the refracting media. The limbs were held in flexion; the tendon reflexes were present and equal and the plantar responses

* Received for publication December 20, 1956.

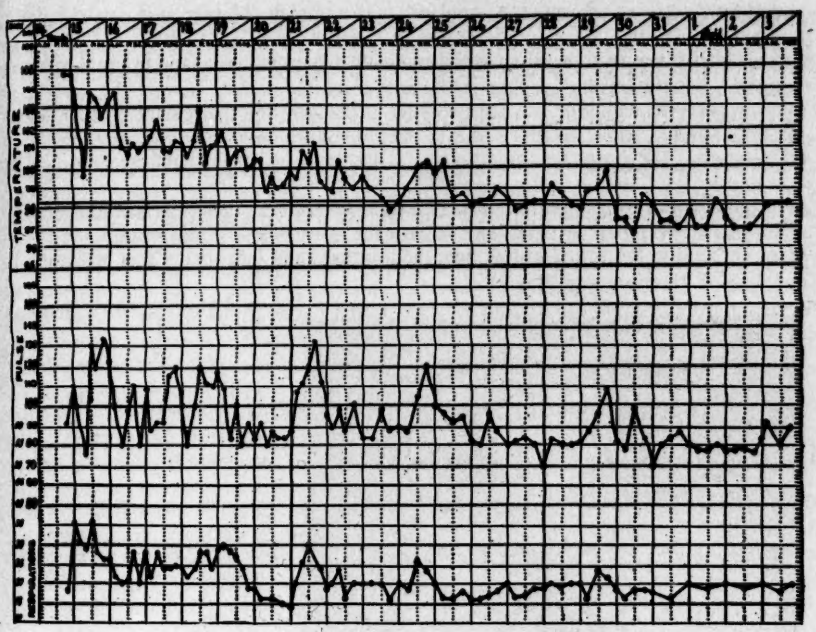

FIG. 1.—Case 1, temperature chart of the first 3 weeks.

flexor. Examination of other systems revealed no abnormality and the spleen was not palpable.

Laboratory Investigations.—Lumbar puncture: opalescent fluid under high pressure containing 4,000 cells/cu.mm., 95 per cent. polymorphs; protein 400 mg. per cent.; no organisms seen in a stained film, sterile on culture.

Haemoglobin 82 per cent.; Haldane (12·14 g. per cent.); white cells 14,100/cu.mm., 85 per cent. polymorphs.

Right conjunctival swab grew many coagulase-positive *Staph. aureus* sensitive to streptomycin, erythromycin, aureomycin, and chloramphenicol, but resistant to penicillin.

Left conjunctival swab: sterile.

Blood culture: *Staph. aureus* with characteristics similar to that isolated from the right eye.

Urine: protein ++, acetone ++, sugar −, many granular and hyaline casts but no cells, culture sterile.

Electrocardiogram: very marked sinus arrhythmia.

Treatment.—The immediate treatment was streptomycin 1 g. twice daily, penicillin 1 mega unit 2-hrly, and heparin 15,000 units subcutaneously 12-hrly. At the first lumbar puncture 20,000 units of penicillin were administered intrathecally. Some hours later, when the characteristics of the organism became known, she was given erythromycin suspension by nasal stomach tube 200 mg. 4-hrly. On the 7th day streptomycin was reduced to 1 g. daily, and on the 14th day streptomycin, penicillin, and heparin were discontinued. The erythromycin was continued until the 24th day, when the temperature had been normal for a week.

Local treatment to both eyes consisted of adrenaline solution (1/1000) and aureomycin cream (1 per cent.) 6-hrly until the 24th day, and atropine 1 per cent. drops daily from the 7th to the 12th day.

The high-potency vitamin preparation "Parentrovite" was injected on alternate days. Tube feeding continued until the 12th day, the patient receiving 1,500 calories of protein, fat,

and carbohydrate in the form of "Complan", with a total fluid intake of about 3·5 l. daily.

Progress.—On the 2nd day the oedema had subsided enough to allow the lids to be parted, when it was seen that there was a complete bilateral internal and external ophthalmoplegia, but the mistiness of the media still prevented a clear view of the fundi. In other respects her condition was substantially unchanged and she remained unconscious until the 6th day, when she first began to obey simple commands and rubbed the site of an injection. There was no response to the flashing of a bright light into the opened eyes and it was feared that vision was lost. All the tendon reflexes were absent except at the ankles, and the plantar responses had become extensor; there was still considerable meningeal and cerebral irritation and at frequent intervals she would scream and throw herself around in the bed. At this time the proptosis and lid oedema was beginning to diminish on the right side (Fig. 2).

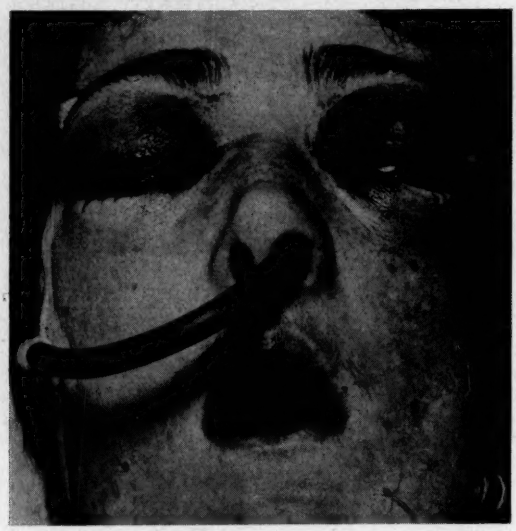

FIG. 2.—Case 1, one week after admission.

The pupils were dilated—even before the atropine, and were unequal, and inactive to light (Fig. 3).

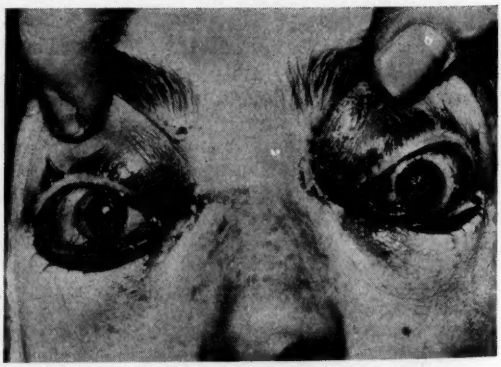

FIG. 3.—Case 1, one week after admission.

The ophthalmoplegia continued and the corneal reflexes remained absent. The fundi were still not clearly visible, but on the 10th day the right one was seen to be normal.

The temperature became normal on the 17th day and, although the patient became more restless and noisy for a period, she regained full consciousness on the 20th day. By this time there was only slight proptosis and minimal chemosis of the right eye and she said that she could see a blurred image with it. The left eye however was still considerably swollen, haziness of the ocular media was still present, and there was no perception of light. The complete bilateral ophthalmoplegia was unchanged, but both corneal reflexes had returned. It was not until the 25th day that the left fundus was clearly seen and the appearances of primary optic atrophy noted.

After the temperature had been normal for 10 days the patient passed a moderate quantity of pus per rectum, and on examination was found to have a boggy mass in the recto-vaginal pouch which was slightly tender. Culture of the pus grew numerous Gram-negative bacilli and enterococci but no staphylococci. This abscess caused no further symptoms and rectal examination a month later was normal.

The proptosis and chemosis had cleared completely by the 6th week, but there was still considerable ptosis. By the time of her discharge from hospital this, too, had almost gone (Figs 4 and 5), although it was still more marked on the left. Seven weeks after the onset of the illness external ocular movements were seen for the first time. Starting as a flicker, upwards in the right and lateral in the left eye, these gradually increased in range and direction until at the time of discharge 6 weeks later they were almost full. Both eyes had normal lateral movements, but elevation and depression were still reduced, more so on the left side. The pupils remained fixed and unequal, larger on the right side. Visual acuity in the right eye was 6/12 correctable to 6/9 and N5, and the visual field was full, but the left eye remained amaurotic.

FIG. 4.—Case 1, 3 months after admission.

FIG. 5.—Case 1, 3 months after admission.

In the 9th week after admission, 3 days before she was due to leave hospital, she developed mild frontal headaches on waking, and the cerebrospinal fluid, which had contained only ten white cells/cu.mm. a month before, was found to contain 57 white cells, 70 per cent. being lymphocytes. Culture was again sterile. A few days later the headaches had become more severe and she developed signs suggesting a right cerebellar lesion. Serial electroencephalograms which had been taken since the 5th week of the illness had shown the gradual reappearance of a stable α-rhythm, and there was no change at this time. X-rays of skull and chest, a white cell count, and the erythrocyte sedimentation rate were normal. It was thought that a cerebellar abscess had developed, and she was given a week's course of oxytetracycline 500 mg. 6-hrly, when the headaches disappeared and the localizing signs gradually decreased. On discharge, on June 17, she was found to have, in addition to the eye signs described above, only a minimal incoordination of the right arm and leg and slightly increased reflexes in the left leg. The cerebrospinal fluid was perfectly normal, containing only one cell/cu.mm. and 15 mg. per cent. protein. When last seen, some 6 months later, she had remained well and all long tract signs had disappeared, although the pupils remained inactive and the left eye was blind. Her mental state was quite normal.

Case 2, a female infant, 2 weeks old, was admitted to St. Thomas's Hospital on February 20, 1956. After a full-term normal delivery she had been breast fed, and on discharge from the maternity hospital 3 days earlier she had been passed as a normal baby, but her mother stated that the child had had a "bad" eye for a week. The day before admission she had been seen in the hospital eye department when an early stye was noted in the upper lid, but there was no chemosis. Chloramphenicol ointment (1 per cent.) was applied three times daily. The next day the eye was more swollen, but the child remained reasonably well and was taking normal feeds until the evening, when she suddenly became comatose and was brought straight up to hospital.

Examination.—The child was comatose and limp. Temperature (axilla) 96·6° F., pulse 140/min., respirations 28/min. There was proptosis and chemosis of the left eye, and the upper lid had a discharging stye and was moderately oedematous. The right eye was normal. Both pupils reacted normally to light, but the fundi were not seen. There was a monilial infection of the mouth. Otherwise no abnormality was revealed except an enlarged spleen.

Laboratory Investigations.—Lumbar puncture: 210 cells/cu.mm., 51 per cent. polymorphs; protein 80 mg. per cent.; sterile on culture.

White cell count: 16,000/cu.mm., 88 per cent. polymorphs.

Blood culture: Heavy growth of coagulase-positive *Staph. aureus* sensitive to all antibiotics tested.

Treatment.—The immediate treatment was streptomycin 250 mg. twice daily and sulphadiazine 250 mg. 6-hrly; 2 days later she received in addition 5,000 units penicillin intrathecally and oxytetracycline 50 mg. 6-hrly. Local treatment to the eyes consisted of sulphacetamide drops (10 per cent.) 2-hrly.

Progress.—The day after admission she appeared to be better and was taking feeds well, but the temperature had risen to 100° F., and on the evening of the second day she had several left-sided epileptic fits. A second sample of cerebrospinal fluid proved sterile, and the fits were controlled with paraldehyde and phenobarbitone, but her condition steadily deteriorated and she died 2 days later.

Post-mortem Examination.—There was thrombophlebitis of the left cavernous sinus and considerable haemorrhage around the neighbourhood of the inferior saggital sinus which extended up the medial side of the hemispheres. The superior saggital and lateral sinuses were normal, but several cortical veins were thrombosed. Multiple areas of

softening, consistent with venous infarction, were seen throughout both hemispheres. There was no evidence of septicaemic spread in any other part of the body.

Discussion

It is important to distinguish between three varieties of cavernous sinus thrombosis since they arise in different ways and have substantially differing prognoses. Two main groups are clearly identifiable:

(1) The aseptic or "marasmic" form, which may occur in the same types of case as does thrombosis in the veins of the limbs or pelvis;
(2) The sinus thrombosis of septic origin.

A further distinction should be made in this latter group, between those cases in which the cavernous sinus thrombus is infected from the start either because the site of infection is adjacent to the sinus or because the thrombus arises by septic emboli, and those cases in which the thrombus in the cavernous plexus is initially free from bacteria, but is liable to develop infection later unless the original septic condition is overcome. It is in this last group, described by Cavenagh (1936) as a chronic compensatory form of the disease, that the great majority of recoveries were recorded before the days of antibiotics.

The second group comprises the acute forms of cavernous sinus thrombophlebitis which used to be almost universally fatal. Eagleton (1926) states that these "present little difficulty in diagnosis; they are early accompanied by chemosis and exophthalmos, first of one eye and then of the other, associated with profound pyaemia, and followed by death from sepsis or a complicating meningitis". In the present examples, there can be little doubt as to the diagnosis in the first case, for it followed this description accurately except for the outcome, and the second case was proved at *post mortem*. However, it is perhaps a sign of the times that, at an early stage, when the oedema was beginning to appear in the second eye, a tentative diagnosis was made in the first case of penicillin-sensitivity. A somewhat similar error was made in a child aged 3 by suspecting nephritic oedema following suppurative otitis media (Reid and McGuckin, 1946). The speed at which the condition progressed was remarkable; one can appreciate the force of the statement "death regularly follows from sepsis in 6 to 48 hours after the involvement of the second eye" (Smith, 1918).

The positive blood cultures obtained from both patients is a frequent finding, Eagleton (1926) citing evidence of blood-stream infection as one of the points upon which the diagnosis rests. On the other hand, the fact that in each case repeated cultures of the purulent cerebrospinal fluid proved to be sterile came as somewhat of a surprise. It appears, however, that this is the usual finding, although it has not been stressed before. Thus in 98 cases collected from the English and American literature since 1920, blood cultures were taken in only 62, but 43 of these (69 per cent.) proved to be positive,

and if one included a further twelve in whom there was evidence of metastatic abscess formation, despite one or more negative blood cultures, the proportion rises to 89 per cent. In only 37 were cerebrospinal-fluid cultures recorded, but 30 of these (81 per cent.) were sterile. Of 26 patients who had both fluids cultured, only two had positive results in both.

The site of infection was in both cases a simple stye. Although these are so common, they very rarely cause cavernous sinus thrombophlebitis. In the 98 cases mentioned above, the original infections were: furuncles of face 53 (nose 25, lip 9, forehead 7, eyebrow 5, cheek 4, chin 3); ear infection 14; sinusitis 13; dental sepsis 8; styes 3; tonsillitis 3; erysipelas 1; facial injuries 1; unstated 2.

One remarkable report deserves special mention: Barnshaw (1939) described a girl of seven who developed typical acute cavernous sinus thrombophlebitis with staphylococcal septicaemia following a stye and made an uninterrupted recovery with expectant treatment only.

The organism responsible in both cases recorded in this paper was *Staphylococcus aureus*. This was the organism found in 70 per cent. of the series described by Shaw (1952). In the 98 cases mentioned above, an organism was isolated in 73: *Staph. aureus* in 67 (92 per cent.), *Strept. pyogenes* in four (5 per cent.), pneumococcus in one (1 per cent), and *Staph. albus* in one (1 per cent.). In view of the rising incidence of penicillin-resistant staphylococci, it is not surprising that cases have been reported due to such organisms (McAllen and Shaw, 1952; Haas, 1955). Both these patients gave cause for considerable anxiety during the course of their illness, and one died later from a cerebral abscess 3 months after an apparently full recovery. In addition, at least five patients have been reported to have died despite penicillin. Three had staphylococcal infections (Abraham, Gardner, Chain, Heatley, Fletcher, and Jennings, 1941; Wolfe and Gain, 1945), and in one the organism was not determined (Fox and West, 1947). In the third a haemolytic streptococcus was grown from nasal discharge (Bennett, 1954), but since treatment was ineffective despite being started comparatively early and this organism is so rarely penicillin-resistant, it is conceivable that a penicillin-resistant staphylococcus was also present.

Such observations suggest that in dealing with a case of acute cavernous sinus thrombophlebitis, one ought not to rely on penicillin alone until the results of bacteriological investigations become known, a matter of at least 12 hours, but should give in addition a broad-spectrum antibiotic as soon as specimens have been taken for culture.

Although heparin was administered in the first case, there is as yet no general agreement on the value of anticoagulant drugs in the treatment of this condition. Lyons (1941) was the first to employ heparin, and it has been given since in several cases. The natural history of the condition, with its progressive thrombophlebitis, would suggest that treatment aimed at preventing further extension of the clot would be of value. On the other

hand, some authors have not used heparin because they consider that the thrombus acts as a protective barrier (Reid and McGuckin, 1946). Such an argument should not be accepted without criticism, since untreated cases usually progress towards a fatal termination with metastatic abscess formation. The thrombus is surely the essential feature of the disease, and one of the criteria of pathogenic staphylococci is that they produce coagulase; moreover, a blood-clot is renowned for the ease with which it becomes infected and for its excellence as a nutritive medium for bacterial growth. As for the suggestion that anticoagulants would encourage wide dissemination of the pathogen, one must remember that, when antibiotics are used, a bacteraemia is less hazardous to life than multiple septic infarcts, which are almost invariably found *post mortem* in fatal cases (Dixon, 1926). Another point was raised by Shaw (1952), who suggested that anticoagulants will give the antibiotic better access to the organisms.

Despite such arguments it is difficult to assess the practical value of anticoagulants in the treatment of the disease, since the past 15 years have also seen the development of antibiotics. It seems, however, that about half the cases treated with sulphonamides or antibiotics as well as anticoagulants have shown evidence of septic emboli, and while a similar proportion of complications has been found in those treated without anticoagulants, several of these died. In the second case described in this paper, when no anticoagulant was used, there was at *post mortem* no sign of active sepsis, but there were multiple cerebral infarcts caused by extension of the thrombosis. On balance then, there does not appear to be any good reason why anticoagulants should not be used, and on general principles they appear to be fully justified.

In the series of 98 cases taken from the literature, eight were treated with antibiotics and anticoagulants with only one death, and that occurred from a cerebral abscess 3 months after apparent full recovery; eighteen cases were treated with antibiotics alone, of which five died in the acute illness. These figures are not conclusive as the recent introduction of anticoagulant therapy might cause a higher proportion of cures by this means to be reported.

The mechanism of the ophthalmoplegia usually found in one or both eyes at the height of the illness, and which in a few cases may only partially resolve, is largely a matter of speculation. Smith (1918) considered that the cause was involvement of the nerves within the cavernous sinus, and stated that the third nerve was most frequently implicated, but that sixth nerve palsies were also often seen, while neuralgic pain might occur in the distribution of the ophthalmic division of the fifth nerve. In the more acute cases he considered that the rising intra-orbital pressure might cause displacement and fixation of the globe and its muscles before any distinct nerve palsies could be recognized. *Post-mortem* reports have been of little assistance, since most record only macroscopic findings. Walsh (1937),

however, reported microscopic findings in six patients. In every case infection of the orbital tissues was found with inflammatory cell infiltration of the muscles; in one case the nerves of one cavernous sinus were invaded with inflammatory cells, and similar changes were seen in the gasserian ganglion in another. In the first patient described above, the return of ocular movements was long delayed as compared with cases recorded in the literature, in which a few days to a week or two seems to be the rule. In our case this took 7 weeks, and although after a further 3 months the external ocular movements are nearly full, the pupils remain inactive. In most recorded cases the pupillary responses were never lost.

Out of the sixty cases which recovered in the above series of 98, blindness in both eyes was the sequel in only one, and blindness in one eye in three. No satisfactory explanation has been suggested for the site or nature of the lesion, or why it should occur in only a few patients. In the present case, disturbance of the refracting media, preventing a clear view of the fundi, persisted in the left eye until the 25th day, when optic atrophy was clearly developing, the original stye having been on the right side. Such a marked disturbance of ocular media has not previously been recorded. Although one might expect to see thrombosis of the retinal veins in cavernous sinus thrombosis, this does not usually occur. One report (Bennett, 1954) records, however, that a few hours before death in the acute illness there were "choked discs and enormous thrombosis of all visible retinal veins". Papilloedema has been reported in a few patients, but the usual description is one of venous congestion with some blurring of the disc. Nicholson and Anderson (1944) reported detailed ophthalmoscopical findings in one patient who developed optic atrophy in the right eye; at the height of the illness the veins were engorged and the arteries were collapsed with extensive sheathing, the disc was moderately swollen, and there was diffuse retinal oedema; 2 months later there was marked optic atrophy. They considered that there had been an inflammatory reaction in the arterial walls, possibly spreading from the cavernous sinus along the arterial wall by direct extension. One suggestion made about the present case was that there might have been an acute glaucoma during the first week of the illness, but the shape of the disc does not support this view. There remain then two possible causes, a "toxic neuritis" of the optic nerve caused by the adjacent purulent inflammation, or an inflammatory arteritis. Histological study of *post mortem* material might give the answer, but opportunities are now exceedingly rare.

A cerebral abscess as a complication or *post mortem* finding is well recognized, being reported in seven out of the series of 98 cases; in five of these it did not appear for from 3 to 6 months after apparent recovery (Lewis, 1934; MacAllen and Shaw, 1952; MacNeal, Frisby, and Blevins, 1941; Wolfe and Gain, 1945). Although the frontal or temporal lobes provide the commoner sites, two cases have been reported of cerebellar abscesses: one on the surface of an hemisphere, the second deep in the midline. In

the first case presented here there was no proof that a cerebellar abscess was present, and, in view of the apparent recovery, the lesion might possibly have been a thrombosis or thrombophlebitis of the veins on the right cerebellar hemisphere.

Summary

(1) Two cases are described of cavernous sinus thrombophlebitis; each arose from a stye, the causative organism being *Staph. aureus*.

(2) In the first patient the complications included meningitis, septicaemia, an abscess in the pouch of Douglas, and possibly a cerebellar abscess. The second patient, an infant of 2 weeks, died.

(3) The diagnosis, treatment, and complications are discussed with reference to the literature.

(4) It is concluded that, in the present state of knowledge, initial treatment should consist of penicillin, a broad-spectrum antibiotic, and anticoagulants.

I wish to thank Dr. J. St. C. Elkington and Dr. J. Forest Smith for helpful advice and for permission to publish the cases.

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OXYPHENONIUM AS AN ATROPINE SUBSTITUTE IN *OPHTHALMOLOGY**

BY

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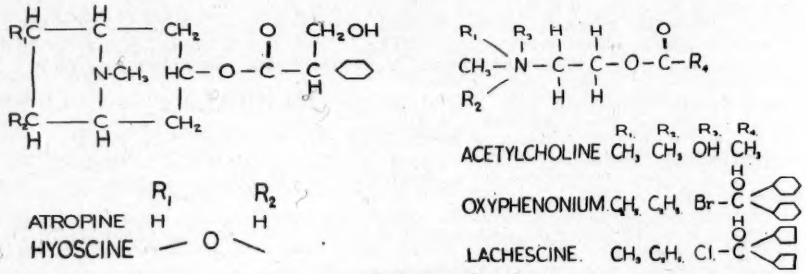
ATROPINE, perhaps the drug most used in ophthalmology, is prone to cause contact-irritation, often at a time when continued mydriasis is essential, in patients on long-term treatment. Unfortunately, most substitutes are less effective in producing mydriasis, and not infrequently contact-irritation is developed to these substitutes in rapid succession.

Lachescine (E3) was developed in Great Britain during the war because of the possibility of a serious shortage of the usual mydriatics. It was found to have an effect mid-way between that of atropine and homatropine with cocaine. Since this time, Lachescine has been found very useful in clinical practice where atropine irritation has occurred. Its difference from the atropine group of mydriatics (Figure) made it almost free from producing irritation. Its usefulness in cases of atropine sensitivity has been suggested in recent ophthalmic text-books, and, in her original article on this subject, Mann (1946) reviews 42 cases of atropine irritation.



FIGURE

When Lachescine was being developed, MacDonald (1947) described the development of Dibutolin in America (Di-n-butylcarbamylcholine). The formula for Lachescine is benzilyl-oxyethyl-dimethyl-ethyl-ammonium chloride.

Now that Lachescine has been withdrawn from production, oxyphenonium (Antrenyl) deserves consideration as an atropine substitute. In fact, it has an action much stronger than that of Lachescine and more prolonged than that of atropine itself.

* Received for publication December 4, 1956.

This article is based on a series of 57 cases treated at the Birmingham and Midland Eye Hospital.

Mydriatic Effect

Experimental work on the mydriatic and cycloplegic effect of oxyphenonium is somewhat contradictory. Plummer, Barrett, Rutledge, and Yonkman (1946) make the following statements:

Two drops of a 2 per cent. solution of Antrenyl instilled at 15-minute intervals into the conjunctival sac of the eye of the rabbit caused no observed mydriasis . . . atropine in 0·5 per cent concentration applied similarly produced maximal pupillary dilatation after two applications.

The mydriatic action of Antrenyl is definitely less marked than that of atropine when each is applied locally to the eye of the rabbit, for a 0·5 per cent. solution of atropine sulphate causes maximal pupillary dilatation, while four times this concentration in Antrenyl produced no obvious changes in pupil size.

These authors conclude that:

Antrenyl possesses less marked mydriatic and anti-salivary activity than atropine.

Havener and Falls (1953) found excellent mydriasis in rabbits, which persisted for 4 to 8 days after a single instillation of 5 per cent. oxyphenonium, and complete mydriasis for 2 days after the instillation of a 1 per cent. solution. They conclude:

In rabbits, the mydriatic effect of oxyphenonium is very much more marked and prolonged than that of atropine; however, the rabbit can detoxify belladonna drugs much more rapidly than can man.

Whatever the conflicting results in rabbits may be, there seems no doubt of the strength of the action of this drug in man. Abrahamson and Hurwitz (1954) state that:

Oxyphenonium mydriasis was slightly more rapid in onset and was completed in the same time as with atropine. Oxyphenonium mydriasis began in 15 to 35 minutes, whereas with atropine it commenced in 20 to 30minutes. The completion time ranged from 35 to 55 minutes with both drugs. Mydriasis with oxyphenonium lasted 15 to 20 days, with atropine 11 to 14 days. The mydriasis was maximal with both drugs.

This statement applies to both mydriasis and cycloplegia but refers to 5 per cent oxyphenonium and 1 per cent. atropine.

Irritant Effects

Although few volunteer this information, most patients, when asked directly, state that the drops sting on instillation, but they are happy to continue with the treatment. A few patients find the drops too painful to use because of burning and notice that the eye flushes after instillation.

In 100 cases treated with a 5 per cent. solution by Abrahamson and Hurwitz

(1954), there was no complaint other than that of a burning sensation, which was severe enough in fourteen cases to lead to the withdrawal of the drug. Other authors (Havener and Falls, 1954) advise against the use of 5 per cent. solutions and have found that 1 per cent. or 0·5 per cent is not irritating to the human eye, and is not strong enough to produce smarting or conjunctival discharge. They have found 1 per cent. solutions of oxyphenonium and atropine comparable in effect.

Report of Cases

57 patients began treatment between May and August, 1956, and these cases were followed until the end of October, 1956. There were 27 males and 30 females, with a slight preponderance of older women of over 60, and of younger men between 20 and 60 years of age. In some of these cases continuous treatment with oxyphenonium was given for over 4 months, fourteen were treated for more than 2 months, and 26 for more than 1 month. At the end of the period of survey, nine patients were still continuing with treatment.

The duration of the condition for which the patients were being treated was less than 1 year in twenty patients, between 1 and 5 years in sixteen patients, and over 5 years in 21 patients.

Oxyphenonium was frequently used when previous irritation had taken place. 39 cases with irritation to atropine or some other mydriatic were treated with oxyphenonium; sixteen of them had previously been treated with Lachescine and were put on to oxyphenonium when the supply of Lachescine became exhausted. Two other cases had been treated with Lachescine without any previous irritation, and in sixteen cases oxyphenonium was used as the first mydriatic.

33 cases had previously had irritation with atropine, twelve with homatropine, four with hyoscine, and three with an antibiotic. In four cases, there had been multiple irritations:

Case 1	(Iridocyclitis)	Homatropine, Lachescine, penicillin, Eumydrin Duboisine, and atropine.
Case 2	(Secondary Glaucoma)	Eserine, Butacaine, homatropine, and hyoscine.
Case 3	(Scleritis)	Atropine, hyoscine, homatropine, and yellow oxide of mercury.
Case 4	(Rosacea Keratitis)	Atropine, homatropine, hyoscine, sulphacetamide and penicillin.

Oxyphenonium proved satisfactory in these cases and produced no irritation, although the length of treatment was 14 weeks, 5 weeks, 2 weeks, and 11 weeks respectively.

In all, there were 10 cases with irritation to more than one drug: in two cases the reaction to oxyphenonium was uncertain from the records, and in the remaining eight it proved satisfactory. Of the other 29 cases, oxyphen-

onium was satisfactory in 23, uncertain in four, and withdrawn because of discomfort in two.

In the whole series of 57 cases oxyphenonium was satisfactory in 45, uncertain in nine, and was withdrawn because of discomfort in three.

One of these was a case of trachoma with recurrent keratitis, previously treated with Lachescine; in this patient oxyphenonium produced the appearances of a chemical conjunctivitis in the lower fornix, with some chemosis.

The other two cases were being treated for uveitis, and oxyphenonium was used after atropine irritation had occurred; these patients complained of discomfort lasting for a few minutes after instillation, and were put on to another mydriatic.

In all the other cases, oxyphenonium proved satisfactory, although in answer to a leading question patients would usually agree that smarting was noticeable on instillation but passed off very soon and was not enough to cause concern. It may be relevant to note that a patient with Behçet's syndrome, had quite marked smarting to begin with, but after 3 months was finding the drops more comfortable; in this case, mydriasis with oxyphenonium was much more satisfactory than with the Lachescine, which had previously been used after atropine irritation. In no case did an irritation occur with a clinical appearance similar to that with atropine, and experience suggests that oxyphenonium is less likely to produce irritation than the other older atropine substitutes.

When treatment is discontinued, mydriasis lasts as long as, if not longer than, with atropine. One patient with hypopyon iritis, who was sensitive to atropine and homatropine, was treated with oxyphenonium 3 times daily from May 31 until August 15, 1956, when mydriasis was discontinued; the pupil was still moderately dilated on October 3, 1956.

In a few cases, oxyphenonium was used as a mydriatic and cycloplegic for refraction in children. Guttae Antrenyl were instilled in one eye and guttae atropine (1 per cent.) in the other. It was found that after a 1 per cent. solution had been used for one or two instillations, atropine produced a greater and more rapid mydriasis, and it was usually necessary to increase the dosage of Antrenyl to 2 per cent. in order to obtain an equal effect. There would seem to be little advantage in using Antrenyl in these circumstances. There is no doubt that it serves its most useful purpose when used as an atropine substitute after irritation has taken place.

In an attempt to overcome the smarting sensation on instillation of the drops, pH and tonicity of oxyphenonium were investigated. It was found that a 1 per cent. Antrenyl solution in distilled water, with 1·35 per cent. boric acid, gave a freezing point depression of 0·526°C., which would make it almost exactly isotonic with the lacrimal secretion. With this preparation the pH was 4·7, but in spite of this acidity the manufacturers thought it would be satisfactory for instillation and would not prove to be particularly uncomfortable. It was, however, felt necessary to include an anti-bacterial

agent, and the drops used in this series were made up as follows: Antrenyl 1 per cent.; benzalkonium chloride 1/5,000; distilled water to 100 per cent., giving a pH of 6·8. Sodium chloride 0·75 per cent. has since been added, to make the drops more nearly isotonic. This gives a freezing point depression of 0·540°C. and a pH of 5·98, and seems more comfortable in use.

Summary

After a brief review of atropine substitutes, a series of 57 cases treated with oxyphenonium is recorded. It is suggested that oxyphenonium is a satisfactory substitute for atropine, particularly in patients showing contact-irritation to atropine and other atropine substitutes.

I wish to thank the consultant staff of the Birmingham and Midland Eye Hospital for permission to make this review of cases under their care, and other members of the staff who have assisted me in obtaining details.

I also thank Ciba Laboratories, who provided the Antrenyl which was used in this series.

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ACCIDENTAL VACCINIA*

BY

CHARLES TAYLOR

Shrewsbury

Case Report

A married woman, aged 25, had been vaccinated in childhood. Her baby was vaccinated on January 6, 1955, and the mother's right eye became irritable on January 19. She was treated by her own doctor with intra-muscular penicillin, sulphathiazole by mouth, and sulphacetamide drops in the eye, and was referred to the Eye, Ear, and Throat Hospital, Shrewsbury, on January 25, 1955.

Fig. 1 shows her condition on admission. There were pustules on the margins of the lids of the right eye, one high up on the right cheek, and one at the muco-cutaneous junction of the right nostril. The right pre-auricular gland was enlarged. She was treated locally with ung. aureomycin, and a drop of atropine was instilled into the conjunctival sac although the cornea was not affected. Chloramphenicol was administered by mouth, and vitamin B complex was given to offset the inhibitive action of the antibiotics on its synthesis in the bowel.

On January 27 the condition had advanced (Fig. 2). The right eye was closed by oedema and a few small pustules appeared in the right temple region (not shown well on the photograph). It was now impossible to see the right cornea. Pustules had appeared at the muco-cutaneous junction of the left nostril and on the lid margins of the left eye. Pre- and post-auricular and cervical glands were enlarged on both sides. A supply of vaccinia gamma globulin was obtained in solid form and reconstituted by the addition of distilled water. 20 ml. were injected intramuscularly on the morning of January 28.

FIG. 1.—Patient's appearance on admission (January 25, 1956).

FIG. 2.—Appearance 2 days later (January 27, 1956).

* Received for publication November 26, 1956.

The patient felt better that evening, and the dose was repeated the next morning, January 29. The small pustules in the right temple region had now disappeared and the lids were much less swollen. The patient felt much better and the temperature had subsided (Table). The dregs in the bottles had some distilled water added and were used locally as

TABLE
TEMPERATURE, PULSE, AND RESPIRATION DURING FIRST 7 DAYS IN HOSPITAL

Date	25	26		27		28		29		30		31	
	p.m.	a.m.	p.m.	a.m.	p.m.	a.m.	p.m.	a.m.	p.m.	a.m.	p.m.	a.m.	p.m.
Pulse	92 92	86	92 98 92	88 88	100 90 90	90 108	100 100	92 80	80 84 80	82 78	84	80 80	82 88
Respiration	20 20	20	20 20 20	20 20	20 22 20	20 20	20 20	20 20	20 20 20	20 20	20	20 20	20 20
Temperature (°F.)	100 100	98·4	101·8 101 100·4	99 98·4	98 100 100	98·6 97	99 99·6	98·6 99	98·4 98 98·6	98·4 97·4	98·4	98 97	97·2 98·4

eyedrops. On January 30 the lesions were dried and crusted and those on the left eyelids had disappeared. The left eye was open and undamaged, and the right cornea could be seen to be unaffected, except for one tiny limbal infiltrate. A crust was removed from one nostril for confirmation of diagnosis.

Fig. 3 was taken on January 31. The lesions cleared rapidly, but some thickness of the lids of the right eye remained. The patient was discharged from hospital on February 16 having been kept perhaps rather longer than necessary (Fig. 4).

FIG. 3.—Improvement seen 4 days later (January 31, 1956).

FIG. 4.—Patient's appearance on discharge (February 16, 1956).

Complications.—Some thickness of the upper lid on the right side remains. There are loss of lashes and epiphora due to scar tissue in the region of the right lower punctum and canaliculus. There is also a small symblepharon towards the inner canthus.

Discussion

Paschen (1932) reviewed the early literature describing accidental vaccinia at many sites. Duke-Elder (1952) sub-divides accidental vaccinia of the eyelids into two groups:

(*a*) the isolated lesion;
(*b*) vaccinia blepharitis.

This case, with additions, falls into the second group. One wonders why the vaccinia spread as it did in this case. It may be argued that the virus is spread by contaminated fingers, but there may also be another explanation:

The spread of vaccinia from the initial site of inoculation, accidental or otherwise is considered to be by way of the blood stream (Ellis, 1935). It has been demonstrated that within 3 to 7 days after vaccination the virus may be present in the naso-pharynx, and that dissemination through the body is haematogenous (Gins, 1929; Collett and Kennedy, 1949).

Watering of the eyes associated with the initial lid lesion on the right side may produce maceration of the skin at the muco-cutaneous junctions of lids and nostrils, and the circumstances thus become akin to the condition of eczema vaccinatum. Some abrasive effect may also be carried out by lid spasm or consciously or subconsciously by wiping, but not necessarily with any contaminated material.

The diagnosis of accidental vaccinia may be simple, but one can imagine circumstances where it might be very difficult (Coriell, Blank, and Scott, 1948). Vaccinia should be considered in the differential diagnosis of any localized, slowly developing vesico-pustular lesion. It may have to be differentiated from syphilis, a simple pyogenic lesion, tubercle, herpes febrilis or zoster, cow-pox, orf, fungus disease, or several tropical lesions.

The diagnosis may be confirmed by culturing the virus on the chorio-allantoic membrane of 10-day-old embryonated chick-eggs (typical plaques being produced on the membrane), or by inoculation of the rabbit cornea with contaminated material (Paul test). Histological sections of the cornea show characteristic basophilic cytoplasmic inclusion bodies of the Guarnieri type (Paul, 1915). A more rapid confirmation may be obtained by examining preparations of pus or scab under the electron miscroscope (Nagler and Rake, 1948).

Among the ocular complications have been described symblepharon, loss of lashes, epiphora, corneal infiltrates and ulcers, disciform keratitis, and rarely retinitis (the last by Franceschetti, 1945).

In an eczematous child the condition of eczema vaccinatum may occur. The mortality rate was described by McKhann and Ross (1938) as 33 per cent. in 1938, so that vaccination or accidental vaccinia in the presence of eczema may be a serious matter.

Treatment.—Various treatments have been recommended: maintenance of cleanliness, application of various antiseptics, administration of ascorbic acid locally and parenterally, and use of antibiotics. Moffatt (1952) described a case of vaccinia of the conjunctival sac treated with vaccinia-immune serum, and suggested there was "prima facie evidence of benefit obtained from the use of immune serum".

This disease may be self-limiting and in many cases, particularly of auto-inoculation, the condition may resolve without complications and with little or no treatment. In other cases, however, resolution may be slow and fraught with danger even to life (as in eczema vaccinatum) and treatment with vaccinia-immune serum or vaccinia gamma-globulin is indicated.

The gamma-globulin is prepared from the plasma of recently vaccinated adults by a special method described by Kekwick and MacKay.

My thanks are due to Dr. Alun Jones, Bacteriologist in the Shrewsbury Group, for his help and advice in confirmation of the diagnosis and treatment, and to the Virus Reference Laboratory, Colindale Avenue, London, N.W.9, for supplying the vaccinia gamma-globulin.

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SYNKINETIC LID RETRACTION*

BY

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ABNORMAL lid retraction of the upper eyelid in congenital ptosis and acquired oculomotor ophthalmoplegia in the phase of its recovery does not appear to be as uncommon as the literature indicates.

The nine cases described in this paper are summarized in the Table.

TABLE

Case No.	Age at Onset (yrs)	Sex	Cause of Ophthalmoplegia	Manifestation
1	47	F	Subarachnoid haemorrhage	Fuchs's phenomenon of lid retraction on adduction Pseudo-Graefe phenomenon of lid retraction on looking down
2	1½	F	Typhoid	Paradoxical retraction on occlusion of sound eye
3	5	M	Head injury	Lid retraction on attempted adduction Pseudo-Graefe phenomenon of lid retraction on looking down Paradoxical retraction on occlusion of sound eye
4	56	M	Syphilis	Lid retraction on attempted adduction
5	Birth	F	Congenital	Lid retraction on occlusion of sound eye
6	Birth	F	Congenital	Duane's retraction syndrome
7	52	M	Myasthenia gravis	Prostigmine-positive lid retraction (uncommon type)
8	Birth	F	Congenital	Lid retraction on attempted adduction and on occlusion of sound eye
9	Birth	F	Congenital	Marcus Gunn phenomenon (even clenching the teeth on the right side with closed mouth caused retraction)

* Received for publication December 3, 1956.

Case Reports

Case 1, a female aged 47 years, first seen on July 28, 1956, developed ophthalmoplegia on the left side following subarachnoid haemorrhage due to a sudden rise in blood pressure in January, 1956. Since then there had been a progressively satisfactory recovery and diplopia persisted only on looking upwards. In the primary position a narrowing of the palpebral aperture was noticed on the left side (Fig. 1A). Elevation of the left globe was defective but all other movements were normal (Fig. 1B). On looking down a pseudo-Graefe phenomenon of lid-retraction was present (Fig. 1C). On looking to the right (*i.e.* on attempted adduction), a wider left palpebral aperture and an exaggerated skin-fold of the eyelid indicated lid retraction (Fig. 1D). The right eye was normal in all respects.

FIG. 1.—Case 1, a female aged 47.

Case 2, a girl aged 5 years, first seen on August 1, 1956, had suffered from typhoid at the age of one year and three months, since when a ptosis of the left upper eyelid had persisted. There was ptosis on the left side in the primary position (Fig. 2A). On occlusion of the right eye, paradoxical lid retraction was present (Fig. 2B). Elevation of the globe was absent on the left side (Fig. 2C). On looking to the right, *i.e.* on attempted adduction, retraction of the left lid was noticeable (Fig. 2D). The right eye was normal.

FIG. 2.—Case 2, a girl aged 5.

Case 3, a boy aged 12, first seen on August 2, 1956, had sustained an injury to the right side of his head by falling on to a hard floor from a height of 16 feet at the age of 5 years. On regaining consciousness after 3 days, he was discovered to have developed ptosis of the right upper eyelid and incomplete movements of the eyeball in all directions. In the following 3 months a certain degree of improvement took place, whereafter the condition remained unchanged. There was ptosis on the right side in the primary position (Fig. 3A). On occlusion of the left eye there was paradoxical lid retraction (Fig. 3B). On looking to the right the ptosis increased (Fig. 3C). Elevation of the right globe was absent and the eye was slightly abducted (Fig. 3D). Adduction of the right eye was absent, and on testing it a retraction of the right lid was seen (Fig. 3E). The pseudo-Graefe phenomenon of lid retraction was present on downward movement of the eyeball (Fig. 3F). The left eye was normal in all respects. In the right eye the vision was reduced to counting fingers at two metres distance, the optic disc was normal, and the pupil was completely paralysed.

FIG. 3.—Case 3, a boy aged 12.

Case 4, a male aged 56 years, first seen on August 3, 1956, had suddenly developed total ophthalmoplegia in June, 1956. The general history of the case, confirmed by a positive serological test, proved syphilis to be the cause. All signs of oculomotor ophthalmoplegia

were absent in the primary position (Fig. 4A). The sixth nerve was paralysed and abduction was absent in the left eye. A wider left palpebral fissure showed a slight but distinct lid retraction (Fig. 4B).

FIG. 4.—Case 4, a male aged 56.

Case 5, a girl aged 15 years, came to hospital on August 10, 1956, for a cosmetic correction of congenital ptosis on the right side. Ptosis was present on the right side in the primary position (Fig. 5A). Elevation of the right globe was absent (Fig. 5B). Paradoxical lid retraction of the right upper eyelid was present on occlusion of the left eye (Fig. 5C).

FIG. 5.—Case 5, a girl aged 15.

Case 6, a girl aged 4 years, was brought to hospital for correction of a convergent squint of about 25°. Examination revealed that this was a case of Duane's retraction syndrome. Abduction of the left eye was absent, and on testing it the left palpebral aperture showed a widening due to lid retraction (Fig. 6A). On looking to the right, adduction of the left eye was restricted, but the globe showed elevation; there was a narrowing of the left palpebral aperture and enophthalmos (Fig. 6B). Recession of the internal rectus was performed, and the cosmetic parallelism of the visual axes in the primary position was excellent (Fig. 6C).

FIG. 6.—Case 6, a girl aged 4.

Case 7, a male aged 52 years, first seen on September 24, 1956, had developed ptosis of the right eyelid 4 months previously. He recovered automatically in 3 weeks without any treatment. He then developed ptosis on the left side, and all laboratory investigations were negative (Fig. 7A).

The patient was made to rest for 10 minutes (or was made to keep looking down on a near object as if reading). After this (or in the morning after sleep), when the patient was asked to look up suddenly, there was a retraction of the ptosed left eyelid (Fig. 7B). Ptosis re-appeared gradually within 5 minutes and the left eye closed completely even while the right eye continued to look upwards (Fig. 7C). An injection of 1 mg. prostigmine showed the retraction of the left eyelid to be due to myasthenia gravis. All other symptoms of the disease were absent (Fig. 7D).

FIG. 7.—Case 7, a male aged 52.

Case 8, a female aged 45 years, first seen on September 29, 1956, had ptosis of the right eyelid dating from birth (Fig. 8A). Adduction was normal on the right side, but looking to the left caused retraction of the right upper eyelid (Fig. 8B). Occlusion of the left eye caused a paradoxical retraction of the right upper eyelid (Fig. 8C).

FIG. 8.—Case 8, a female aged 45.

Case 9, a female aged 32 years, first seen on October 23, 1956, was a typical case of the Marcus Gunn phenomenon. There was congenital ptosis of the left eyelid (Fig. 9A). On opening the jaw there was lid retraction on the left side (Fig. 9B). With a closed mouth, if the patient clenched her teeth on the right side, or moved the lower jaw to the right, there was retraction of the left eyelid (Figs 9C and 9D). The ptosis was enhanced when the lower jaw was moved to the left (Fig. 9E).

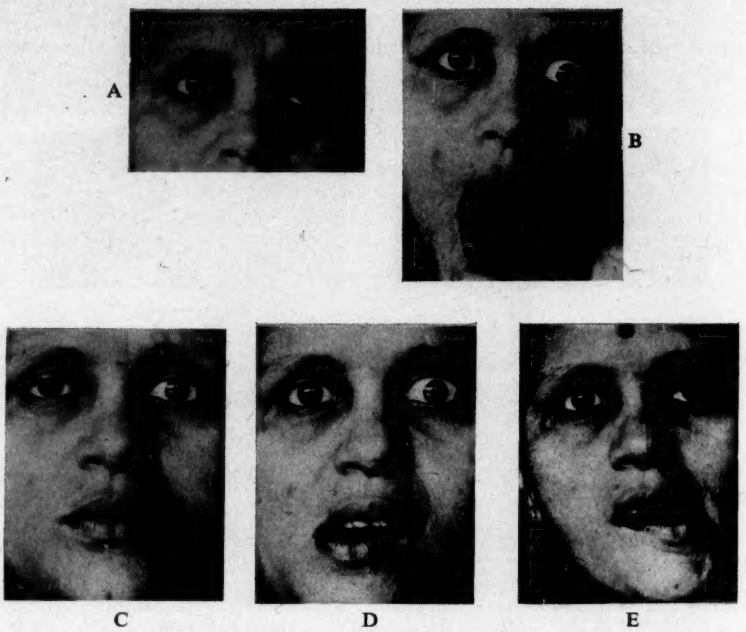

FIG. 9.—Case 9, a female aged 32.

Discussion

Abnormal lid retraction of several types was seen in the nine cases described above. In three cases (1, 3, and 8) more than one variety was seen.

Paradoxical lid retraction on occlusion of the sound eye was congenital in two cases (5 and 8) and was an acquired lesion in two others (2 and 3), in which it was due to typhoid and head injury respectively.

Fuchs's phenomenon of retraction on attempted adduction was present in Case 8 (congenital) and also in Cases 1, 2, and 3 (in which it was due to subarachnoid haemorrhage, typhoid, and head injury, respectively). The condition was present on attempted abduction in one case of ophthalmoplegia after syphilis (Case 4).

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The pseudo-Graefe phenomenon was not seen as a congenital lesion in this series, but occurred in two cases (1 and 3) after subarachnoid haemorrhage and head injury respectively.

The Marcus Gunn phenomenon (Case 9), Duane's retraction syndrome (Case 6), and myasthenia gravis (Case 7) were also seen as single entities.

Case 3 deserves special mention, since it presents an example of Fuchs's phenomenon and the pseudo-Graefe phenomenon combined, with paradoxical lid retraction on occlusion of the sound eye. This rare combination does not appear to have been reported in the literature.

Summary

Nine cases of abnormal lid retraction are reported, the lesions being congenital in four cases, and acquired in five cases.

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CORRESPONDENCE

PARADOXICAL LID RETRACTION IN UNILATERAL CONGENITAL PTOSIS

To the Editorial Committee of the BRITISH JOURNAL OF OPHTHALMOLOGY

SIRS—The interesting case described and illustrated by Jain, Sethi, and Parkash (*British Journal of Ophthalmology*, 1956, **40**, 558), shows several points characteristic of a congenital superior rectus palsy, where the resulting vertical deviation has in the course of time become largely concomitant. The ptosis on the affected side is a pseudo-ptosis, disappearing when the affected eye looks straight ahead instead of downwards. The "paradoxical" lid retraction on the unaffected side is the normal elevation of the upper lid accompanying the normal elevation of a healthy eye.

It is not uncommon for the affected eye in a case of congenital superior rectus palsy to be habitually used for fixation when the patient is looking downwards, and this explains why the visual acuity has been retained. The unaffected eye is normally responsible for fixation in all other directions, hence the reappearance of the ptosis when the unaffected eye is uncovered.

Yours faithfully,

G. J .O. BRIDGEMAN
T. KEITH LYLE

6 DEVONSHIRE PLACE,
LONDON, W.1.
21 *December*, 1956.

BOOK REVIEWS

An Atlas of Diseases of the Eye. By E. S. Perkins and P. Hansell, 1957. Pp. 91, figs. Churchill, London. (42*s*.)

As stressed by Sir Stewart Duke-Elder in the foreword, the only satisfactory way to study medicine is by the constant observation of patients.

However, when time is limited, as in teaching undergraduates, it is often difficult to present to a class a comprehensive cross-section of common disorders. The problems in finding an intricate case of iritis, let alone one of Coats's disease, are well known to all teachers.

This new atlas of eye diseases will greatly help in filling up these gaps. It consists of about two hundred beautiful illustrations, the great majority in colour, with a brief but adequate description of the condition on the adjacent page. The external conditions of the eye are illustrated by colour photography, with certain features accentuated by the artist, and the internal conditions by fundus photography or painting; the standard is such that it is sometimes quite difficult at first glance to distinguish the two.

Reproduction is by eight-colour photo-lithography on fine quality cartridge paper, and the result must be one of the finest productions in medical literature. The process is costly and it is no surprise to learn that the sale price represents only one-tenth of cost, the remainder being generously subsidized by Roche Products Limited.

With this Atlas, the undergraduate and medical practitioner can quickly become acquainted with the eye. The student of ophthalmology can quickly revise his knowledge of the clinical appearance of eye diseases, and the ophthalmologist will find the book of great assistance in his teaching.

Because of the costly process, the atlas is not fully comprehensive, and this is the only criticism. Squints, for instance, are not fully appreciated by many practitioners, but this subject is not included.

It is obvious that great trouble has been taken in the collection of material and its illustration; the result is worthy of the effort.

Endogenous Uveitis. By Alan C. Woods, with illustrations by Annette Smith Burgess, 1956. Pp. 303, 123 figs, (42 col.), bibl. Baillière, Tindall and Cox, London. (£5).

In the confused state of our knowledge concerning the aetiology of uveitis it is refreshing to have such an authoritative and clear statement of opinion as is provided by this book. The subject matter covers the classification, pathology, diagnosis, and treatment of endogenous uveitis, excluding such conditions as lens-induced uveitis, heterochromic iritis, and septic inflammations of the eye.

As was to be expected from the originator of the classification, uveitis is divided into granulomatous and non-granulomatous types; a distinction which many ophthalmologists find difficult to apply in practice and one which presupposes a type of aetiology which often cannot be substantiated. Professor Woods admits the validity of these criticisms but claims that the classification is so firmly ingrained in the literature that to substitute another terminology would cause endless confusion.

Apart from this question of classification the book can be highly recommended. The section on the aetiology and pathogenesis of the granulomatous cases shows the change in emphasis that has taken place in recent years. In 1941 tuberculosis accounted for 79 per cent of cases and syphilis for 16 per cent; in 1953 toxoplasmosis (acquired and congenital) accounted for 26 per cent of cases, tuberculosis for only 22 per cent, and syphilis for 7 per cent, with sarcoidosis 6 per cent and brucellosis 7 per cent. The largest group consisted of the miscellaneous and undetermined cases, 31 per cent.

The theories of allergy and tissue hypersensitivity are clearly described in relation to the pathogenesis of the non-granulomatous cases. The symptomatology and pathology of those types of uveitis in which invasion of the eye by organisms is proven includes some interesting observations on helminthic, virus, and fungus infections.

The remainder of the book deals very fully with the diagnosis and search for aetiological factors, with a suggested scheme of investigation for individual cases. That this involves no little work on the part of the investigator and considerable fortitude from the patient can be judged from just one test involving no less than sixty cutaneous reactions to strains of streptococci.

Therapy is dealt with at considerable length and the description of the use of corticosteroids is particularly valuable. Physical methods, non-specific protein therapy, chemotherapy, and desensitization methods are also detailed.

The bibliography is extensive and the histological illustrations are excellent. The book is well printed and has an adequate index.

NOTES

Oxford Ophthalmological Congress, 1957

The Oxford Ophthalmological Congress will assemble at Balliol College, Broad Street, Oxford, on June 30, 1957, and meetings will be held on July 1, 2, and 3 in the Lecture Hall of the School of Physiology, South Parks Road, Oxford.

The Doyne Memorial Lecture will be delivered on July 2 by Dr. Derrick Vail (*Chicago, U.S.A.*).

A discussion on the Facial Neuralgias will be introduced by Mr. E. F. King (*London*), Dr. W. Ritchie Russell (*Oxford*), and Mr. G. F. Rowbotham (*Newcastle*). A discussion on the Rehabilitation of the Blind and Partially Sighted Patient will be opened by Dr. Dorothy R. Campbell (*Coventry*), Professor W. J. B. Riddell (*Glasgow*), and Mr. T. S. Drake (*Principal, America Lodge, Torquay*).

Members wishing to contribute to these discussions or to submit papers on other

subjects should send their names to the Honorary Secretary as soon as possible. Members are also invited to forward questions for debate in an Any Questions Session.

Ophthalmologists not already members of the Congress who wish to attend the meetings should communicate with the Honorary Secretary; there is no entrance fee or annual subscription but a fee of three guineas is payable for attendance at the Congress.

IAN C. FRASER.
Honorary Secretary and Treasurer.

21 Dogpole,
SHREWSBURY.

OBITUARY

CHARLES LEONARD GIMBLETT

Mr. Charles Leonard Gimblett died in the Westminster Hospital on January 21, 1957, at the age of 66, after a relatively short illness, the culmination of two previous serious illnesses.

He was born on June 19, 1890, the only son of Robert Wheddon Gimblett of Somerset, and was educated at Clifton College, and at Gonville and Caius College, Cambridge, where he took the Natural Sciences Tripos. He obtained his clinical training at St. Thomas's Hospital, qualifying in 1914. He graduated M.B., B.Ch., the following year and entered the Royal Navy, where he subsequently had charge of the eye departments of the Royal Naval Hospitals at Portland and Chatham. He graduated M.D. in 1918, and became M.R.C.P. in 1919, and F.R.C.S. in 1922. He returned to St. Thomas's Hospital when the war ended and held an impressive series of house appointments including senior house surgeon in the Eye Department, where he came under the influence of Fisher and Hudson, whose sayings he often quoted. He was appointed honorary ophthalmic surgeon to the Royal Northern Hospital and honorary assistant surgeon at the Royal Westminster Ophthalmic Hospital in 1923; 5 years later he was appointed full surgeon at the latter and gave up his appointment at the Royal Northern.

He became senior surgeon at the Royal Westminster Ophthalmic Hospital in 1947 just before the amalgamation with Moorfields and the Central London Hospital.

He was also elected Vice-President of the Ophthalmic Section of the Royal Society of Medicine.

As in all things, having decided to specialize in ophthalmology early in his career, his preparation for the task ahead was very thorough.

In his earlier years he worked as chief clinical assistant at Moorfields where he came in contact with Claud Worth, whose teaching on squint impressed him deeply and led to a permanent interest in orthoptics and the treatment of squint. The outcome was the establishment of the Orthoptic Department at the Royal Westminster Ophthalmic Hospital in 1930 with Miss Maddox as orthoptist and himself as surgeon-in-charge. A training school for orthoptists was started and Gimblett realized the necessity of placing the training on a sound footing. He was instrumental in obtaining recognition for orthoptists as Medical Auxiliaries, and became the first chairman of the British Orthoptic Board, which was formed in 1934 to control the standard of training, hold examinations, and grant diplomas.

Gimblett was a rather shy man and not given to extolling his own prowess, but he was lavish in his praise of others when he thought they deserved it. He was tremendously fond of children and had a ready fund of stories and conundrums with which to amuse his younger patients thus enabling him to start an examination in an atmosphere of confidence and friendship. He was inordinately kind to his patients by whom he was universally beloved and who will mourn his loss deeply. He was an excellent chairman in committee, and his charming sense of humour was always a joy to his friends and colleagues.

Apart from his professional work he was greatly interested in mediaeval art and antique furniture of which he was an excellent judge. His marriage to Audreen McNicol in 1935 proved a most happy union. He delighted in taking his family to the Mull of Kintyre where he could enjoy an out-door life and have a "sailing" holiday. To his widow and two sons, his many friends and colleagues will extend their deepest sympathy in their sad loss.